The Arylation of 2-Pyrones and Related Heterocycles

Aisling M. Prendergast, B.Sc.

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Supervisor: Dr. Gerard P. McGlacken

Head of School: Prof. Justin D. Holmes

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Science is built up with facts, as a house is with stones; but a collection of facts is no more a science than a heap of stones is a house.

Henri Poincaré

Declaration

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism.

_____ _____

Aisling M. Prendergast Date

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For my Granda

Abstract

2-Pyrones, and related heterocycles such as 2-pyridones, 2-coumarins and 2-quinolones, are useful model substrates to test a novel methodology due to their varied chemical properties. In addition, these moieties possess broad spectrum biological activity. Chapter 1 provides a review of C–H activation methodology as it has been applied to 2-pyrones and related heterocycles.

Direct arylation *via* C–H activation of 2-pyrone, 2-pyridone and 2-coumarin compounds is described in Chapter 2. Protocols for the palladium-catalysed direct arylation of these molecules were developed and applied to a library of substrates. C–H activation at both the C–3 and C–5 positions of the 2-pyrone scaffold was achieved. The C–5 direct arylation methodology proceeded with retention of a C–Cl bond to give a cyclised 3-chloro-2-pyrone.

In Chapter 3, the development of cross-coupling conditions for the cyclised 3-chloro-2-pyrone is discussed. Following on from this, more generally applicable, environmentally friendly cross-coupling conditions evolved to allow the application of green chemistry principles to the Suzuki-Miyaura cross-coupling of 2-coumarins, 2-pyrones, 2-pyridones and 2-quinolones, with yields of up to 99%.

In parallel to the synthetic aspects of this project, investigations were also performed to understand the mechanisms through which 2-coumarins and related heterocycles undergo C–H activation and direct arylation reactions. In Chapter 4 the experiments which were performed as part of these investigations are described, and the results are presented. Based upon these results from three different sets of reaction conditions, it was proposed that C–H activation of these substrates occurs *via* concerted metallation-deprotonation.

Preface

This thesis contains work which has been published after peer-review, or which is in the process of publication. A full list of publications arising from this thesis is provided in Appendix I.

Abbreviations and Acronyms

Å	ångström
Ac	acetyl
acac	acetylacetonate
AcOH	acetic acid
AMLA	ambiphilic metal-ligand assistance
amu	atomic mass unit
anal.	analysis
approx.	approximately
aq	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br s	broad singlet
Bu	butyl
c	centi (10^{-2})
°C	Celsius degrees
^{13}C NMR	carbon nuclear magnetic resonance
calcd	calculated
cataCXium®A	di(1-adamantyl)-*n*-butylphosphine
CDC	cross-dehydrogenative coupling
CMD	concerted metallation-deprotonation
cod	cyclooctadiene
COSY	correlation spectroscopy
Cp	cyclopentadienyl
Cy	cyclohexyl
δ	NMR chemical shift
d	doublet
D	deuterium
DavePhos	2-dicyclohexylphosphino-2′-(*N,N*-dimethylamino)biphenyl
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N*′-dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublets of doublets
deg	degree
DEPT	distortionless enhancement by polarisation transfer
DFT	density functional theory
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide

DPEPhos	(oxydi-2,1-phenylene)bis(diphenylphosphine)
dq	doublet of quartets
d.r.	diastereomeric ratio
dt	doublet of triplets
DTBP	di-*tert*-butylperoxide
E	energy
e.g.	for example
ECP	electric core potential
EDG	electron-donating group
ee	enantiomeric excess
equiv.	equivalent(s)
e.r.	enantiomeric ratio
ESI	electrospray ionisation
Et	ethyl
et al.	and others
EWG	electron withdrawing group
FT-IR	Fourier-transform infrared spectroscopy
g	gram(s)
GC	gas chromatography
h	hour(s)
h	Planck's constant (6.626×10^{-34} J s)
^{1}H NMR	proton nuclear magnetic resonance
HetAr	heteroaryl
HMBC	heteronuclear multiple-bond correlation spectroscopy
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation spectroscopy
Hz	Hertz
i	iso
i.e.	that is
IR	infrared
IRC	intrinsic reaction coordinates
J	coupling constant
k	rate constant
KIE	kinetic isotope effect
L	litre
LDA	lithium diisopropylamide
lit.	literature
LRMS	low resolution mass spectrometry
µ	micro (10^{-6})
m	metre
	milli (10^{-3})
	multiplet
m	meta
M	metal
	molar
m/z	mass-to-charge ratio
max	maximum

m-CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MePhos	2-dicyclohexylphosphino-2′-methylbiphenyl
mg	milligram
MHz	megahertz
min	minute
	minimum
mL	millilitre
mmol	millimole
mol	mole
	molecular
mol%	mole percent
m.p.	melting point
Ms	methanesulfonyl, mesyl
MS	mass spectrometry
MTBE	methyl *tert*-butyl ether
MW	microwave
ν_{max}	frequency of maximum absorption
n	nano (10^{-9})
n	normal
*n*BuLi	*n*-butyllithium
NBS	*N*-bromosuccinimide
NBO	natural bond orbital
NCS	*N*-chlorosuccinimide
N. D.	not determined
NIS	*N*-iodosuccinimide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
NPs	nanoparticles
o	ortho
o/n	overnight
π	type of orbital, electron
p	para
PCC	pyridinium chlorochromate
Ph	phenyl
PhD	Doctorate of Philosophy
PIDA	phenyliodo(III)diacetate
PivOH	pivalic acid
$PivO^-$	pivalate
PMB	*p*-methoxybenzyl
ppm	parts per million
Pr	propyl
p-TsOH	*p*-toluenesulfonic acid
q	quartet
RDS	rate-determining step

R factor	reliability factor
(R,S)-Rev-Josiphos	(2*S*)-1-[(1*S*)-1-(Dicyclohexylphosphino)ethyl]-2-(diphenylphosphino)ferrocene
r.t.	room temperature
RuPhos	2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
s	second
	singlet
σ	type of orbital
S_EAr	electrophilic aromatic substitution
sec, *s*	secondary
SET	single-electron transfer
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	triplet; time
t, tert	tertiary
T	temperature
TBAB	tetrabutylammonium bromide
TBHP	*tert*-butyl hydroperoxide
TBPB	*tert*-butyl peroxybenzoate
TBDPS	*tert*-butyldiphenylsilyl ether
TCCA	trichloroisocyanuric acid
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
TFA	trifluoroacetic acid, trifluoroacetate
TFAA	trifluoroacetic acid anhydride
TfO	triflate, trifluoromethanesulfonate
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMS	tetramethylsilane
	trimethylsilyl
TOF LC-MS	time-of-flight liquid chromatography-mass spectrometry
Tol	tolyl
Ts	4-toluenesulfonyl, tosyl
UV	ultraviolet
W	weak
Wt	weight
XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
ZPE	zero point energy

Note: For the coumarin framework, the 2- nomenclature (*i.e.* 2-coumarin) is not required. However, it is used throughout this thesis to demonstrate the similarity with the 2-pyrone, 2-pyridone and 2-quinolone. The 2- nomenclature is required for these frameworks.

Chapter 1: Introduction

Every person you meet knows something you don't; learn from them.

H. Jackson Brown Jr.

1.1. Preface

This chapter will consist of a manuscript entitled "Transition Metal-Catalysed C–H Activation of 2-Pyrones, 2-Pyridones, 2-Coumarins and 2-Quinolones" which will be submitted as a Microreview to the *European Journal of Organic Chemistry* in 2018. Consequently, sections of the chapter such as the abstract and introduction may contain repeating concepts and paragraphs.

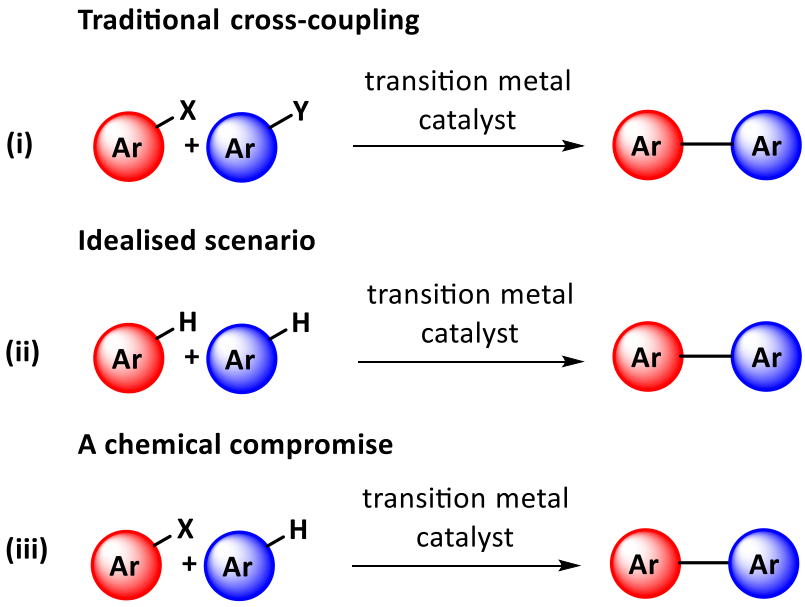
1.2. Abstract

C–H activation has emerged as a viable alternative to traditional C–C bond forming reactions such as the Suzuki-Miyaura, Stille, Negishi and others. However, C–H activation is rarely employed in total synthesis or fine chemical manufacture, particularly as an end-game strategy. This may be due to the harsh conditions typically required. For C–H activation to become a truly useful and versatile methodology, conditions must emerge which are applicable to compounds with multiple functionalities. In this review, we hope to inspire the chemistry community to focus their efforts on milder conditions for C–H activation and cross-dehydrogenative coupling. To this end, we have focused on describing C–H activation as it has been applied to several classes of biologically interesting, but chemically sensitive motifs: the 2-pyrones, 2-pyridones, 2-coumarins and 2-quinolones.

1.3. Introduction

The formation of aryl–heteroaryl bonds is a very important transformation in organic synthesis[1] due to the abundance of this moiety in natural products and pharmaceuticals.[2] The most widely used methods for the construction of this structural unit involve Suzuki-Miyaura,[3-5] Stille,[6-8] and Negishi[9-10] couplings, and similar reactions (**Scheme 1.1 (i)**).[11] More recently, direct arylation protocols which involve at least one C–H activation[12-15] event, and offer a number of advantages over traditional cross-coupling, have emerged.[16-20] For example, the installation of activating groups is bypassed, and the production of waste (*e.g.* B, Sn or Zn based) is eliminated. In an idealised scenario (**Scheme 1.1 (ii)**),[21] both coupling partners are unactivated, with the only by-products being hydrogen gas (H_2) or water (H_2O). One

impediment to the widespread application of C–H activation methodology is the development of regioselective methods, as in the majority of cases a number of C–H bonds are available for activation. Thus it can be troublesome to control and predict regioselectivity, and directing groups are often needed to guide the transition metal into position and facilitate smooth reactivity.[22] A chemical compromise is sometimes required (**Scheme 1.1 (iii)**), whereby one of the preactivated coupling partners is replaced with a simple arene.



Scheme 1.1. Approaches to C–C bond formation.

Alongside the development of oxidative cross-couplings catalysed by second- and third-row transition metals (Pd, Rh, Ru, etc.), first-row transition metal species have been discovered where single-electron transfer (SET) processes usually dominate. The regioselectivity in these radical-mediated reactions depends on the electronic nature of the potential reaction sites. The promising area of radical-mediated C–H activation and cross-coupling has recently been reviewed.[23]

This review will focus on C–H activation reactions which have been reported to proceed *via* an organometallic mode of action, as distinct from direct functionalisation reactions which occur *via* mechanisms involving oxidation and SET. Several general mechanistic modes for transition metal-mediated C–H activation

processes have been proposed, such as electrophilic aromatic substitution (S_EAr),[24-25] concerted metallation-deprotonation (CMD),[26-35] and σ-bond metathesis.[36-37]

For C–H activation to become a truly usable and versatile methodology, it must become a protocol applicable to compounds with multiple functionalities. C–H activation is a seldom-used methodology in total synthesis, especially in late-stage functionalisation,[38] which reflects the harsh conditions typically required.

As emphasised by Glorius,[39] a major hurdle to the application of a new chemical methodology to real synthetic problems is a lack of information regarding its application beyond the idealised conditions of the seminal reports. By highlighting the strategies and conditions employed in the C–H activation of several chemically sensitive but biologically important motifs: 2-pyrone,[40-43] 2-pyridone,[44] 2-coumarin[45-47] and 2-quinolone[48-50] (**Figure 1.1**), we hope to inspire other chemists to target their research towards milder reaction conditions for C–H activation so that it can become a truly useful synthetic tool. Due to the varied reactivity which can be displayed by these moieties (*vide infra*), they are excellent model compounds for the application of C–H activation in total synthesis.

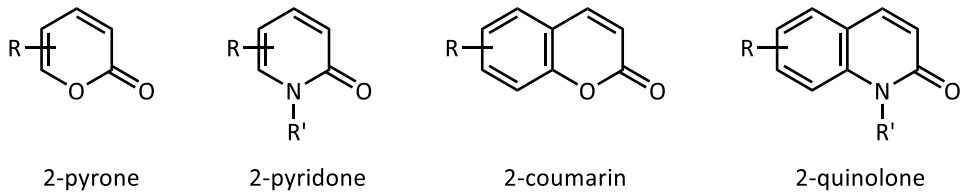


Figure 1.1. Biologically important substrates.

In this review, reactions involving the organometallic C–H activation of 2-pyrones, 2-pyridones, 2-coumarins and 2-quinolones will be discussed with relevant examples. It will be further subdivided based on the metal employed, and organised chronologically within each subsection.

1.4. C–H activation of 2-pyrones

2-Pyrones are good model systems with which to test new methodologies, as they can possess aromatic,[51] diene[52-53] and enone[54-55] properties and they have been shown to ring-open under some cross-coupling conditions (**Figure 1.2**).[56]

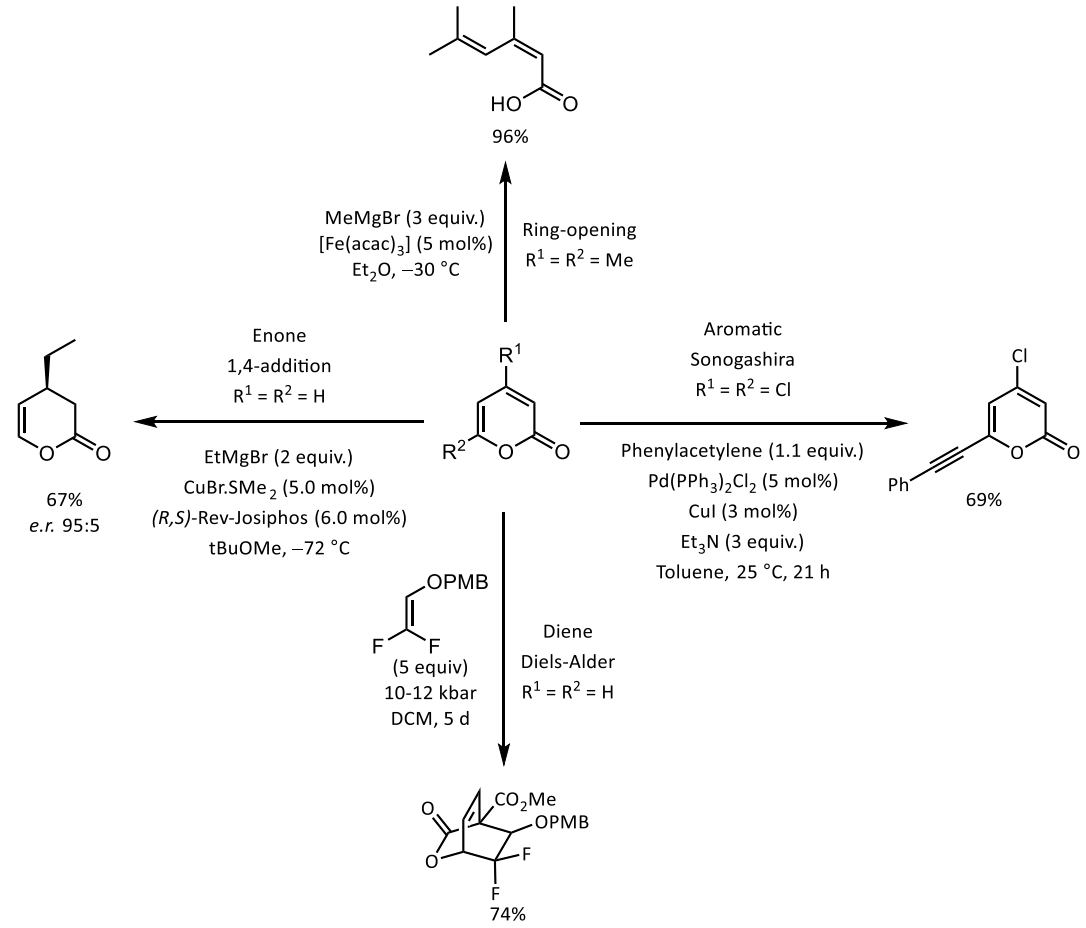


Figure 1.2. Multiple functionality of 2-pyrones.

Additionally, 2-pyrones are a privileged biological scaffold[43] which have been shown to possess broad spectrum bioactivity, including antifungal, antibiotic and cytotoxic effects.[40-42] For example, bufadienolides such as bufalin (**Figure 1.3**) are an important group of compounds characterised by a 2-pyrone connected to a steroid nucleus. The bufadienolides can have diverse biological effects, including cardiac poisoning in animals and inhibitory activity towards leukaemia cell lines.[42]

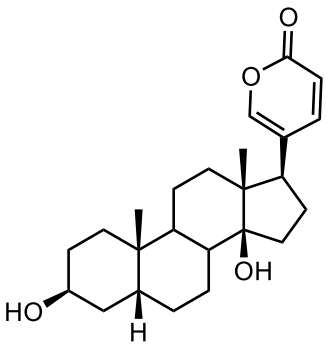
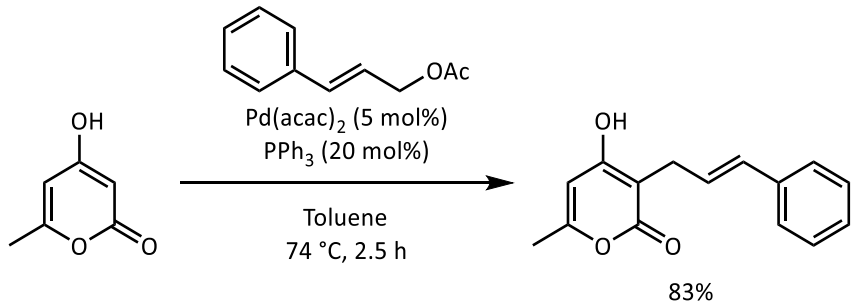


Figure 1.3. Bufalin.

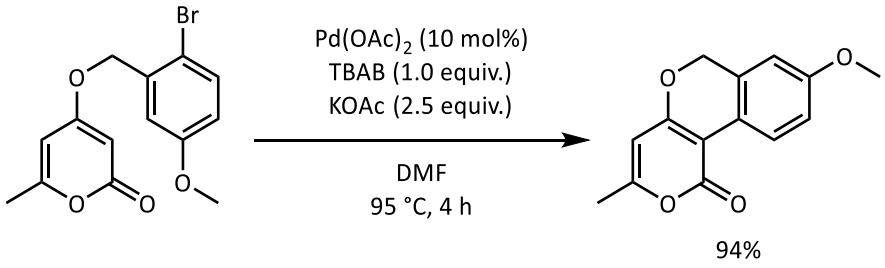
1.4.1. Palladium-catalysed C–H activation

Moreno-Mañas reported the palladium-catalysed alkylation of 2-pyrones with allylic systems in 1988,[57] which was proposed to occur *via* an initial reversible O-alkylation at C–4, followed by C–alkylation at C–3 (**Scheme 1.2**).



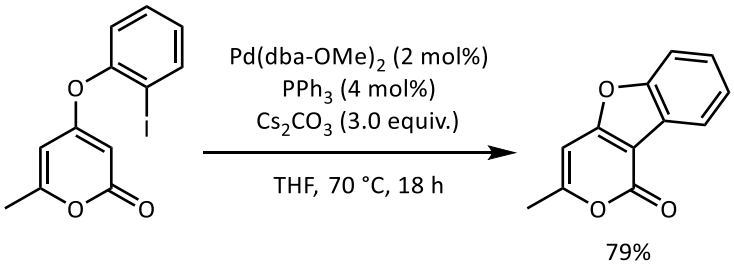
Scheme 1.2. Palladium-catalysed alkylation of 2-pyrones.

Majumdar described the intramolecular direct arylation of 2-pyrones and 2-pyridones using palladium catalysis (**Scheme 1.3**).[58] The reported conditions offered advantages over an existing methodology utilising tin hydrides *via* a proposed radical mechanism.[59]



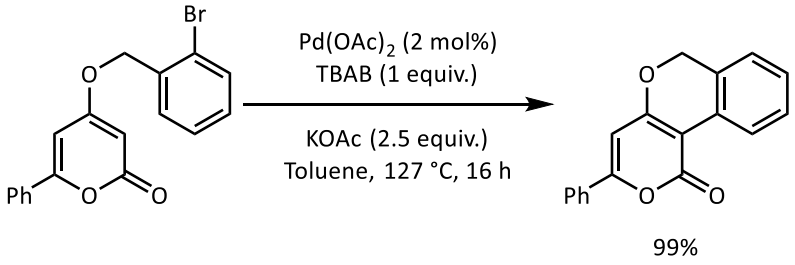
Scheme 1.3. Palladium-catalysed intramolecular arylation of 2-pyrones.

Fairlamb reported a similar intramolecular regioselective C–H functionalisation of 2-pyrones (**Scheme 1.4**).[60] This reaction was also successful with a bromide on the aryl ring, and a variety of substitutions on the aryl ring were tolerated, except for electron-withdrawing groups which led to a reduction in yield. Substitution of the 6-Me group by H, Ph and CH_2CH_2Ph did not hinder the reaction. A Heck-type mechanism involving carbopalladation of the 2-pyrone framework was proposed.



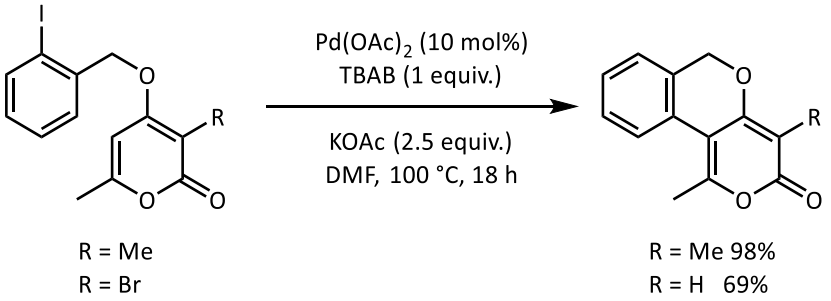
Scheme 1.4. Intramolecular direct arylation of 2-pyrones.

C–H activation of 2-pyrone substrates to give six-membered heterocycles has been reported by Fairlamb and McGlacken (**Scheme 1.5**).[61] Reaction at C–3 was completely regioselective when the substituent at C–6 was more sterically demanding than a methyl group. When a methyl group was present at C–6, up to 21% of the C–5 cyclised product could be isolated. The authors proposed that catalysis occurred *via* a 16-electron [Pd(0)L_2X] intermediate (where L is most likely solvent) derived from Pd(0) colloidal clusters stabilised by the tetrabutylammonium bromide (TBAB) salt. DFT calculations modelling a CMD C–H activation were utilised to examine the experimentally observed regioselectivity. It was shown that C–3–H activation was favoured over C–5–H activation, but that C–5–H activation remained accessible.



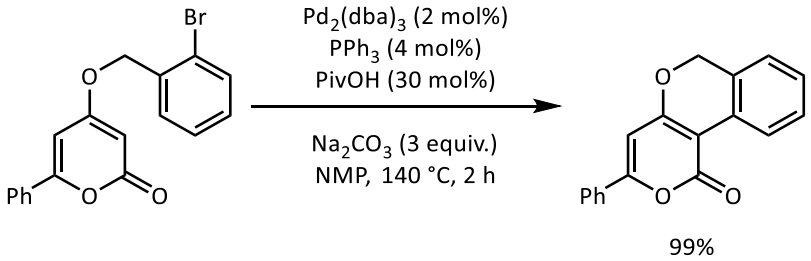
Scheme 1.5. Intramolecular direct arylation to give six-membered rings at C–3 under modified Jeffery's conditions.

They also found that reaction at C–5 could be forced to occur if the C–3 position was blocked with a methyl group or a bromine (**Scheme 1.6**). The methyl blocking group gave an excellent yield of the C–5 coupled product, but this blocking group cannot be easily removed or further functionalised. Surprisingly, when a bromine was used as the blocking group, hydrodebromination of the C–5 cyclised product occurred.



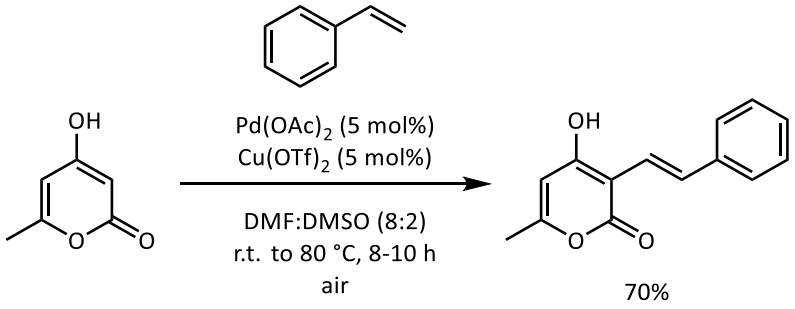
Scheme 1.6. Intramolecular direct arylation to give six-membered rings at C–5 under modified Jeffery's conditions.

McGlacken reported a second set of conditions for C–H activation of 2-pyrone substrates to give six-membered rings (**Scheme 1.7**).[62] These conditions were proposed to involve a homogeneous Pd species using PivOH as a necessary co-catalyst.[61] A CMD mechanism was proposed. A variety of substituents at C–6 were well tolerated, and the reaction was regioselective for the C–3 position. The exception to this involved an electron-withdrawing group *para* to the site of oxidative addition, which led to reduced regioselectivity and the C–5 cyclised product was isolated.



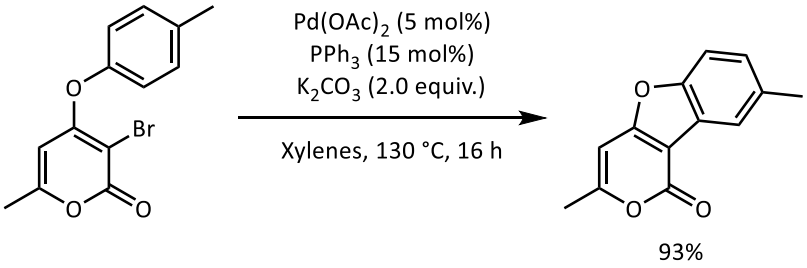
Scheme 1.7. Intramolecular direct arylation to give six-membered rings under CMD conditions.

Palladium-catalysed direct dehydrogenative C–3 alkenylation of 2-pyrones was described by Lah in 2015 (**Scheme 1.8**).[63] The reported methodology was regioselective for alkenylation at C–3 over C–5 in keeping with the trend of 2-pyrone C–H activation processes. The yields were remarkably consistent across the reported substrate scope.



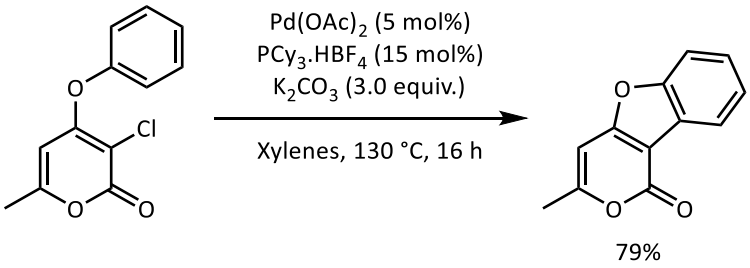
Scheme 1.8. Dehydrogenative alkenylation of 4-hydroxy-2-pyrones.

McGlacken reported the Pd-catalysed intramolecular direct arylation of 3-bromo-2-pyrones (**Scheme 1.9**).[64] These conditions were successfully applied to twelve 2-pyrone substrates in moderate to excellent yields, including electron-poor aryl rings. A kinetic isotope effect of 3.3 for the cleavage of the aryl C–H bond was reported for the C–H activation reaction in the same paper, and a CMD mechanism was proposed.



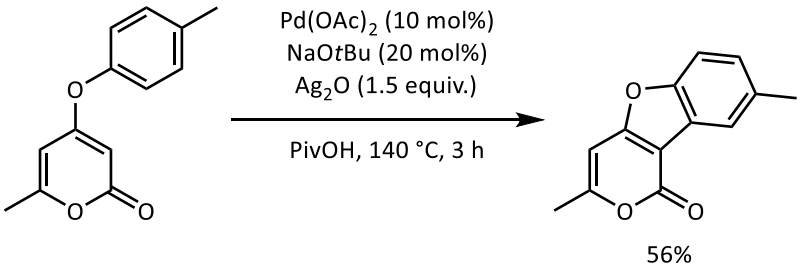
Scheme 1.9. Intramolecular direct arylation of 3-bromo-2-pyrones.

This report also utilised 3-chloro-2-pyrones as substrates. A change in phosphine ligand and an increased loading of base were required (**Scheme 1.10**).[64] The conditions were applied to three 2-pyrone substrates in good to excellent yields. By installing the halide on the 2-pyrone framework rather than on the aryl ring, a broader substrate scope was accessible through substituted phenols, which are more cost-effective than the corresponding halogenated phenols.



Scheme 1.10. Intramolecular direct arylation of 3-chloro-2-pyrones.

McGlacken reported the double C–H activation, or cross-dehydrogenative coupling (CDC), of eight 2-pyrone substrates (**Scheme 1.11**).[65] Despite the presence of two available sites for C–H activation on the 2-pyrone at C–3 and C–5, exclusive C–3–H activation was observed in all cases.

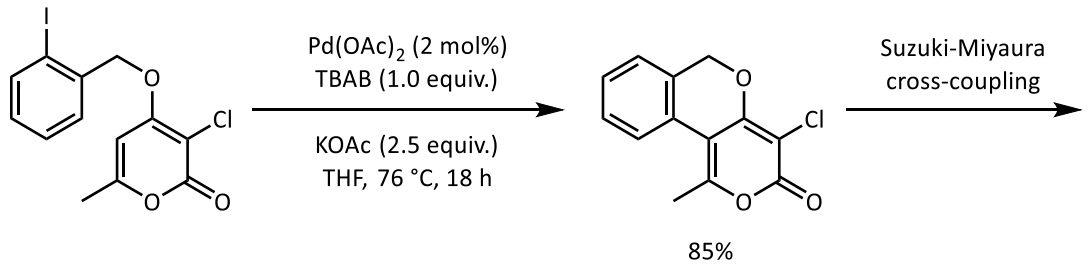


Scheme 1.11. Double C–H activation/cross-dehydrogenative coupling of 4-phenoxy-2-pyrones.

Chen and Xu reported the synthesis of indolo[3,2-*c*]pyrones from 4-aniline substituted 2-pyrones by CDC (**Scheme 1.12**).[66] The catalytic system is mild and base-free, tolerating a range of phenyl-subsituted substrates to give *N*-unprotected products in good to excellent yields.

Scheme 1.12. Cross-dehydrogenative coupling of 4-anilino-2-pyrones.

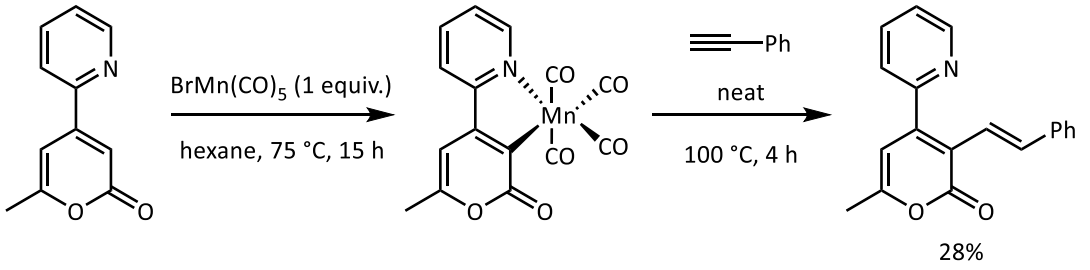
To our knowledge, with the exception of McGlacken's 2014 report,[61] all Pd-catalysed C–H activations of 2-pyrones have shown preferential reactivity towards C–3 functionalisation. Recently, McGlacken and co-workers disclosed a direct arylation protocol which allowed access to C–5 cyclised products (**Scheme 1.13**).[67] A C–Cl bond was retained at C–3 during the direct arylation process which allowed for further derivatisation at C–3. This was demonstrated with a Suzuki-Miyaura cross-coupling reaction.



Scheme 1.13. Intramolecular direct arylation to give six-membered rings at C–5 with retention of C–Cl bond.

1.4.2. Manganese-mediated C–H activation

Lynam and Fairlamb have reported the first Mn(I)-catalysed C–H activation of 2-pyrones.[68] A highly reactive manganacycle was detected and characterised. The intermediate product is effective for hydride transfer to alkenylated products, or reductive elimination to pyridinium products. An excess of phenylacetylene was required to favour hydride transfer over reductive elimination (**Scheme 1.14**). These observations provided the first evidence of manganacycles as key intermediates in Mn(I)-catalysed C–H activation processes involving substrates containing directing groups.



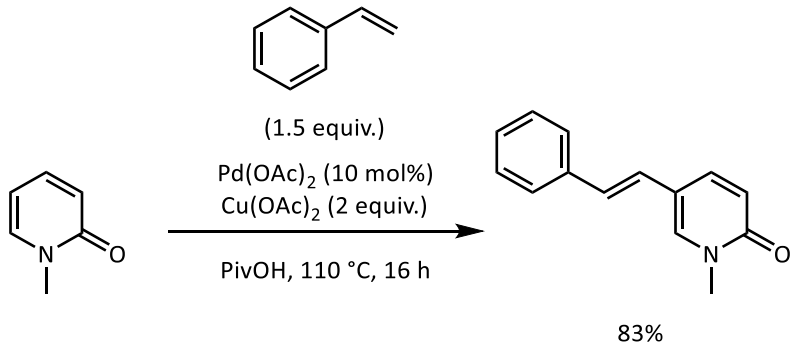
Scheme 1.14. Manganese(I)-mediated C–H activation of 2-pyrones.

1.5. C–H activation of 2-pyridones

2-Pyridones are isosteres of 2-pyrones, but could potentially ligate to metal catalysts *via* the nitrogen atom. The 2-pyridone moiety is an attractive target for synthetic chemists as a number of biologically active molecules contain this structural unit.[44] The 2-pyridone skeleton is present in many natural compounds which possess antibacterial and antifungal activity.[44] 2-Pyridone derivatives are key intermediates in the synthesis of pyridine, piperidine, quinolizidine and indolizidine alkaloids.[69]

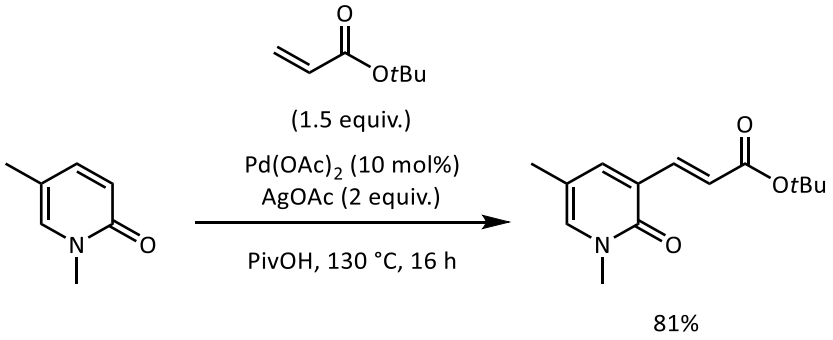
1.5.1. Palladium-catalysed C–H activation

Li has described the mono-olefination of 2-pyridones at the C–5 position *via* Pd-catalysis with $Cu(OAc)_2$ as the oxidant (**Scheme 1.15**).[70]



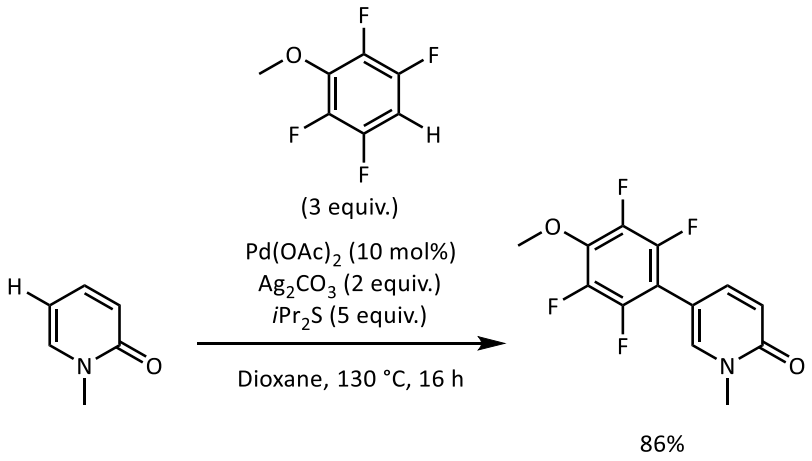
Scheme 1.15. C–5 olefination of 2-pyridones *via* C–H activation.

In the same report, the olefination of 2-pyridones at C–3 was achieved when C–5 was blocked with a bromo, alkyl or aryl group (**Scheme 1.16**).[70] It was necessary for there to be an electron-withdrawing group on the olefin coupling partner. Sequential diolefination was also achieved under similar conditions.[70]



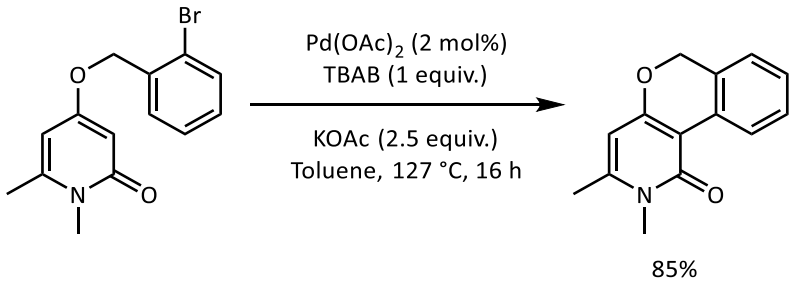
Scheme 1.16. C–3 olefination of 2-pyridones *via* C–H activation.

The CDC of 2-pyridones was also reported by Li in this paper (**Scheme 1.17**).[70] The observed reactivity was similar for the olefinations and for the CDC of 2-pyridones and polyfluorinated arenes. Sequential diolefination was observed, but diarylation could not be achieved. The authors comment that the aryl-aryl cross-coupling appears to be both more sterically and electronically demanding than the corresponding olefination, and that the initial arylation should significantly deactivate the pyridone ring such that no further electrophilic C–H activation can be achieved.



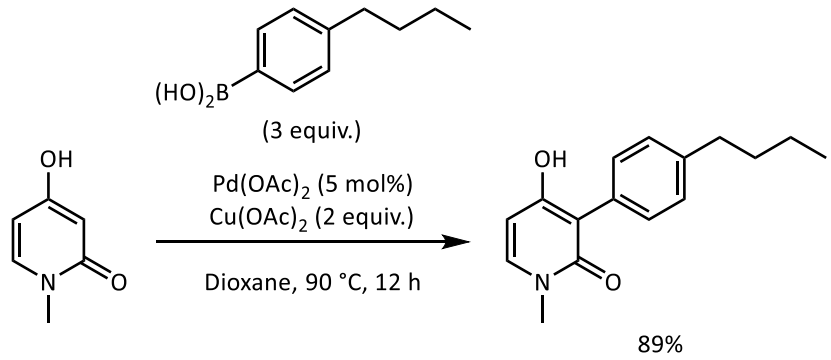
Scheme 1.17. The arylation of 2-pyridones *via* cross-dehydrogenative coupling.

Fairlamb and McGlacken reported the intramolecular direct arylation of 2-pyridones under modified Jeffery's conditions (**Scheme 1.18**).[61] Interestingly, the conditions which were optimised for a 2-pyrone substrate (**Scheme 1.5**) were directly applicable to the corresponding 2-pyridone. Exclusive reaction at C–3 was observed.



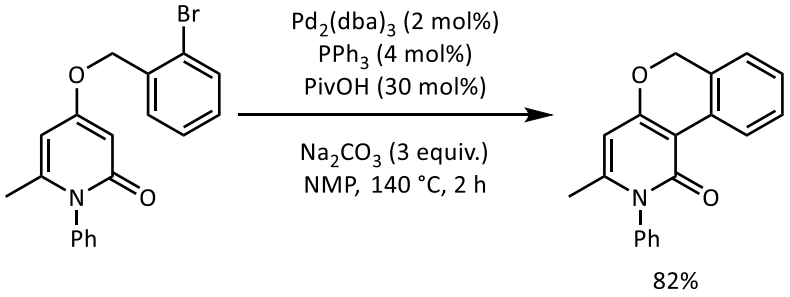
Scheme 1.18. Intramolecular direct arylation of 2-pyridones to give six-membered rings under modified Jeffery's conditions.

The first example of palladium-catalysed direct arylation of 2-pyridones with aryl boronic acids at C–3 was reported by Zografos (**Scheme 1.19**).[71] This is a powerful and efficient method for the rapid construction of 3-aryl-4-hydroxy-2-pyridones. Informative kinetic experiments utilising NMR spectroscopy were used to study the undesired homocoupling of the 2-pyridone. It was shown that the formation of the C–3–Pd complex was reversible in the absence of K_2CO_3, and that there was a synergistic effect of the base on the formation of the dipyridone side-product. These experiments informed the suppression of this undesired side-product through the exclusion of K_2CO_3 from the reaction.



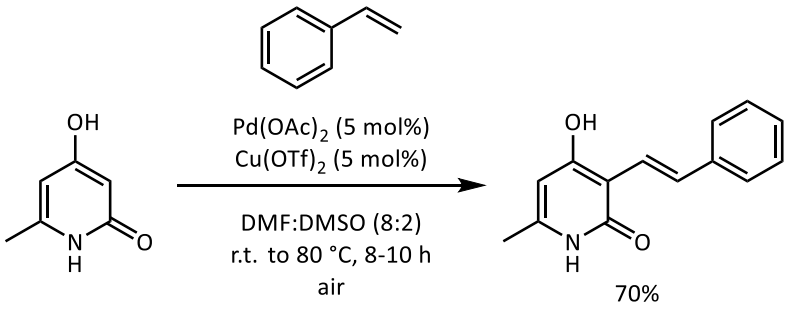
Scheme 1.19. Direct arylation of 2-pyridones *via* C–H activation.

McGlacken reported the intramolecular direct arylation of 2-pyridones (**Scheme 1.20**).[62] Again, exclusive reaction at C–3 was observed. The reaction is reported to proceed *via* a CMD mechanism. Notably, the conditions which were optimised for a 2-pyrone substrate (**Scheme 1.7**) gave good yields for related 2-pyridone substrates.



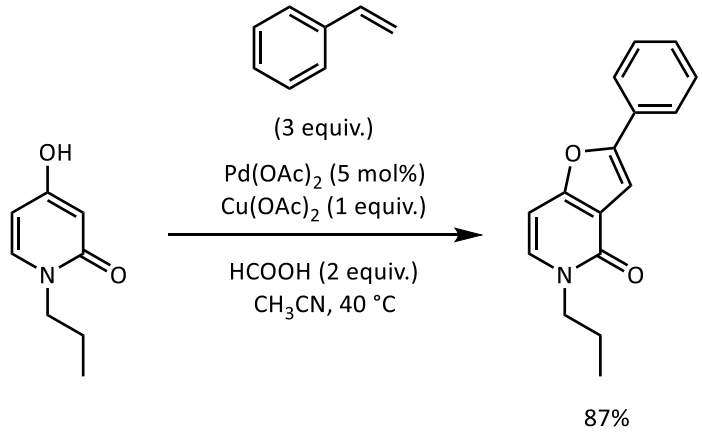
Scheme 1.20. Intramolecular direct arylation of 2-pyridones to give six-membered rings under CMD conditions.

Regioselective C–3 alkenylation was observed by Lah for 4-hydroxy-2-pyridones (**Scheme 1.21**).[63] This represents the first direct 3-alkenylation of 4-hydroxy-2-pyridones. The conditions required a catalytic quantity of $Cu(OTf)_2$, which presumably acts as a co-oxidant with air.



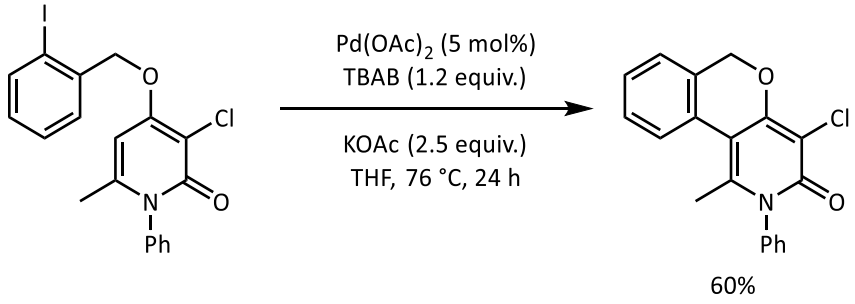
Scheme 1.21. Dehydrogenative alkenylation of 2-pyridones.

The direct alkenylation of 2-pyridones was independently reported by Zografos (**Scheme 1.22**).[72] In this case, under similar conditions, 3-alkenyl-4-hydroxy-2-pyridones are also formed when using higher substituted alkenes. However, when terminal alkenes are used, intermediate Pd–O formation leads to a further reaction, and the efficient production of furo[3,2-*c*]-pyridinones. The authors suggest that the catalytic cycle starts with the direct activation of 4-hydroxy-2-pyridone by Pd(II), in line with their previous observations.[71] Migratory insertion of the pyridone-palladium species to the alkene, followed by reductive elimination gives the Pd(0) and the product. Depending on the substrate, the product can undergo further oxidation, as is the case in **Scheme 1.22**. Pd(0) is proposed to undergo oxidation by $Cu(OAc)_2$ back to Pd(II) to reenter the catalytic cycle.



Scheme 1.22. Sequential direct alkenylation and oxidation of 2-pyridones *via* C–H activation.

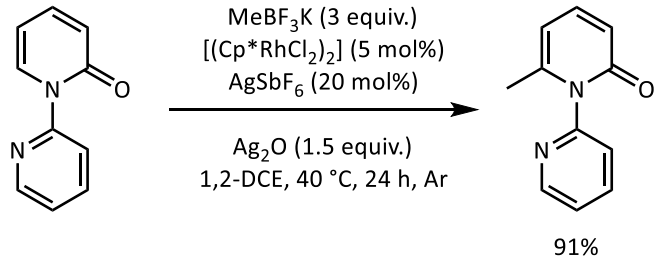
Recently, McGlacken and co-workers disclosed a direct arylation protocol which allowed access to C–5 cyclised 2-pyrones with retention of a C–Cl bond (**Scheme 1.13**).[67] In contrast to a previous study by the same group,[61] the methodology was successfully extended to 2-pyridone substrates (**Scheme 1.23**).[67]



Scheme 1.23. Intramolecular direct arylation to give six-membered rings at C–5 with retention of C–Cl bond.

1.5.2. Rhodium-catalysed C–H activation

Liu described the 2-pyridine-directed, rhodium-catalysed C–H alkylation of 2-pyridones with a wide variety of alkyl and cycloalkyl trifluoroborate reagents (**Scheme 1.24**).[73] The reaction proceeded with excellent regioselectivity and functional group tolerance. Importantly, a protocol for subsequent removal of the *N*-pyridyl directing group was reported.



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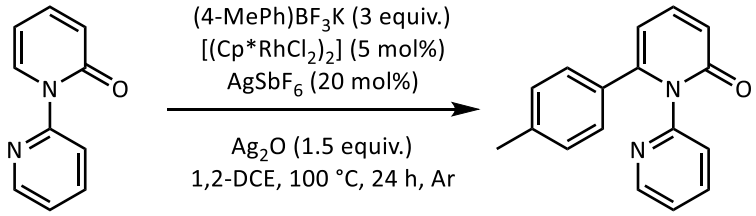
Scheme 1.24. Direct alkylation of 2-pyridones *via* C–H activation.

Direct arylation at C–6 could also be achieved using Liu's conditions, although higher temperatures were required (**Scheme 1.25**).[73]



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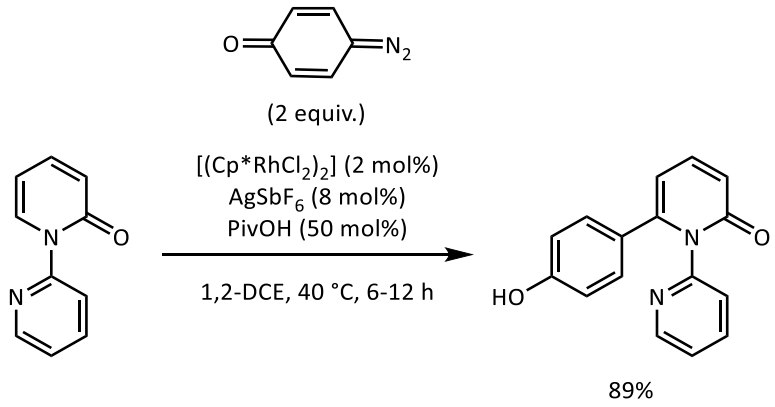
Scheme 1.25. Direct arylation of 2-pyridones *via* C–H activation.

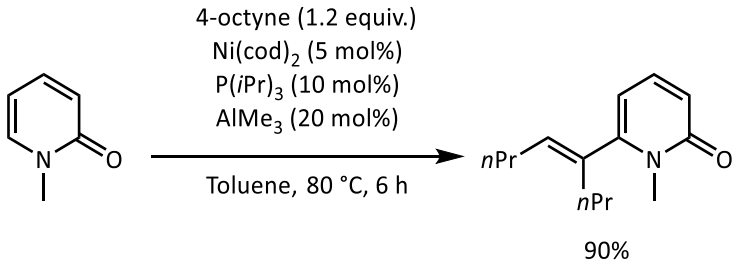
Direct arylation at C–6 of 2-pyridones was achieved by Samanta with quinone diazides under Rh(III) catalysis (**Scheme 1.26**).[74] The authors proposed that a cationic Rh(III) species coordinates to the 2-pyridyl directing group on the nitrogen of the 2-pyridone, then undergoes pivalate-assisted CMD to furnish a rhodacycle intermediate. The rhodacycle could then react with the quinonediazide to generate a metal-carbenoid intermediate with extrusion of N_2. Migratory insertion of Rh, followed by protonation and rearomatisation would give the product and regenerate the active Rh(III) catalyst.



Scheme 1.26. Direct arylation of 2-pyridones *via* C–H activation.

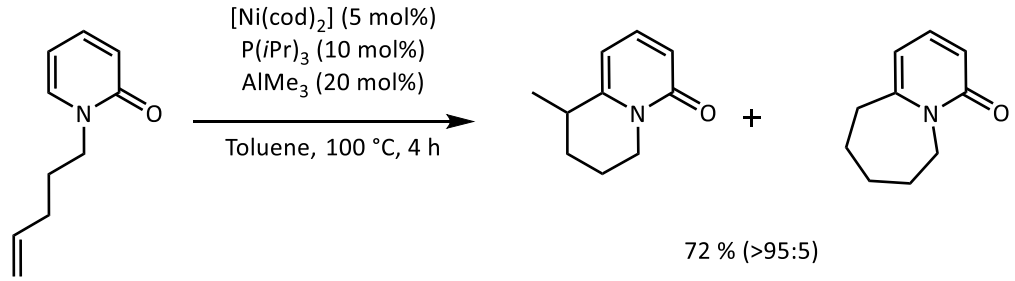
1.5.3. Nickel-catalysed C–H activation

Nakao and Hiyama described the alkenylation of 2-pyridones by nickel catalysis (**Scheme 1.27**).[75] Unusually, the transformations allow functionalisation at the 6-position of 2-pyridones in the absence of a directing group.



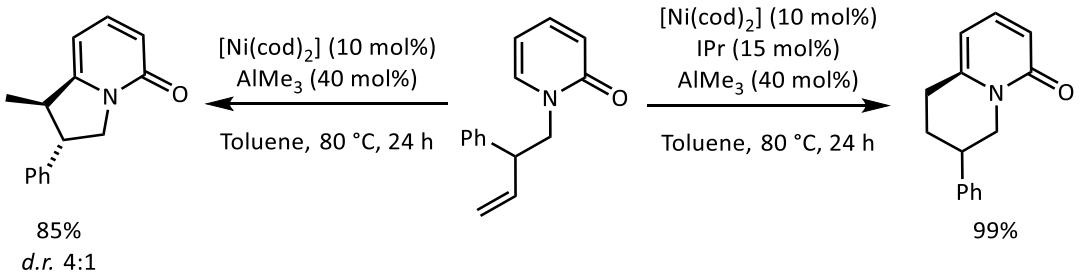
Scheme 1.27. Nakao and Hiyama's direct alkenylation of 2-pyridones *via* C–H activation.

Intermolecular alkylation using terminal alkenes could not be achieved under Nakao and Hiyama's conditions. However, intramolecular addition across tethered terminal alkenes proceeded mainly in an exo-trig fashion to give bicyclic products (**Scheme 1.28**).[75]



Scheme 1.28. Intramolecular alkylation of 2-pyridones *via* C–H activation.

An exquisitive nickel-catalysed C–H functionalisation of 2-pyridones and subsequent cyclisation to 1,6-annulated 2-pyridones by selective intramolecular olefin hydroarylation was reported by Cramer.[76] The switch between the exo- and endocyclisation modes was controlled by two complementary sets of ligands. Irrespective of ring size, the regioselectivity of the cyclisation fell under full catalyst control (**Scheme 1.29**).



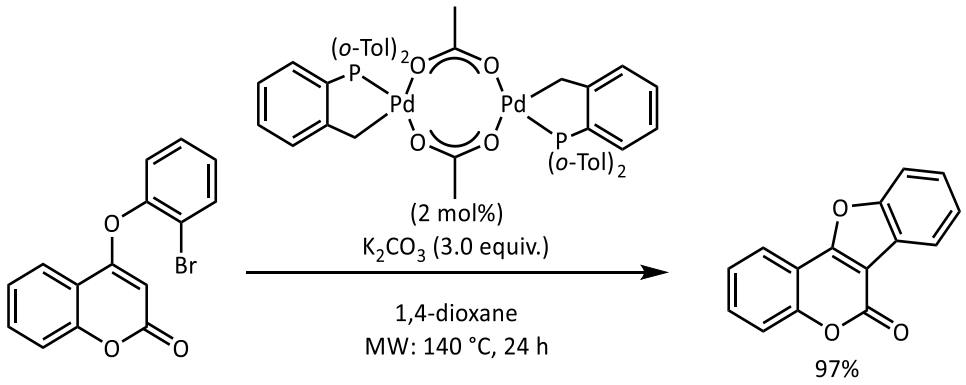
Scheme 1.29. Intramolecular olefin hydroarylation of 2-pyridones *via* C–H activation.

1.6. C–H activation of 2-coumarins

2-Coumarins are structurally related to 2-pyrones, but the presence of an aromatic ring can confer additional stability compared to the 2-pyrone framework. The low toxicity of naturally-occurring 2-coumarins and their broad pharmacological properties are attractive to medicinal chemists as a source of novel therapeutic agents. The pharmaceutical industry, in particular, is deeply aware of this important moiety in the search for new drug candidates, as discussed by Proença and co-workers in a review of the biological importance of structurally diversified 2-coumarins in 2016.[77]

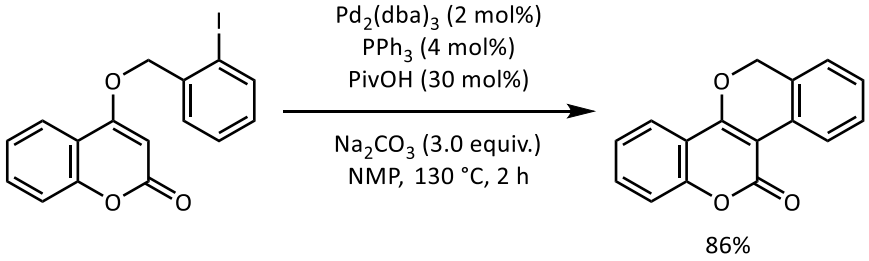
1.6.1. Palladium-catalysed C–H activation

Kapdi reported the microwave-assisted intramolecular direct arylation of 4-(2-bromophen)oxy-2-coumarins (**Scheme 1.30**) using a phospha palladacycle.[78] The palladacyclic complex shown was found to be the most active of those screened for promoting the transformation.



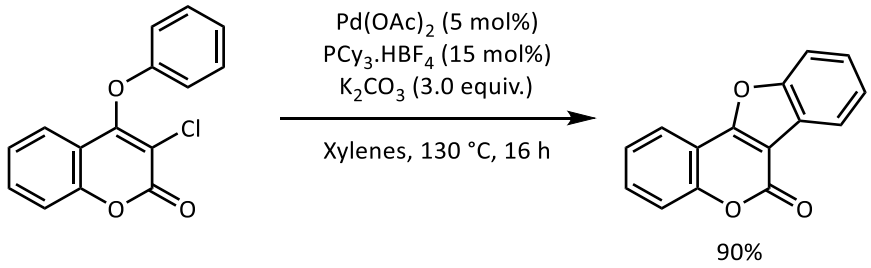
Scheme 1.30. Intramolecular direct arylation of 2-coumarins.

McGlacken reported the intramolecular direct arylation of 4-(2-iodobenzyl)oxy-2-coumarins (**Scheme 1.31**) after optimising the reaction conditions on the related 2-pyrone scaffold (**Scheme 1.7**).[62] The reaction was proposed to proceed *via* a CMD mechanism. Mechanistic experiments, including the isolation of an oxidative addition intermediate, were performed with the 2-coumarin substrate which demonstrated the requirement for PivOH in the success of the reaction.



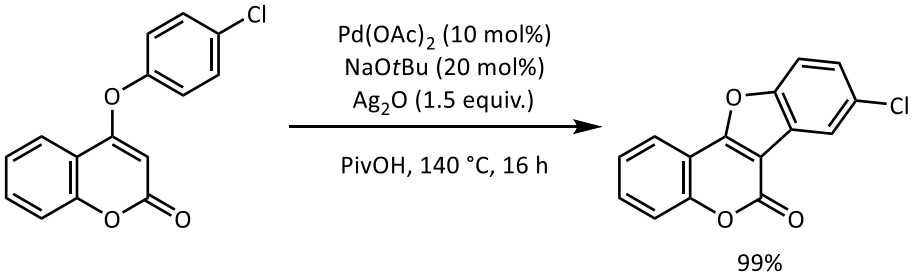
Scheme 1.31. Intramolecular direct arylation of 2-coumarins.

The same group described the intramolecular direct arylation of 3-chloro-2-coumarins to gain access to the coumestan family of compounds (**Scheme 1.32**), using conditions which had been optimised for the 2-pyrone substrate (**Scheme 1.10**).[64]

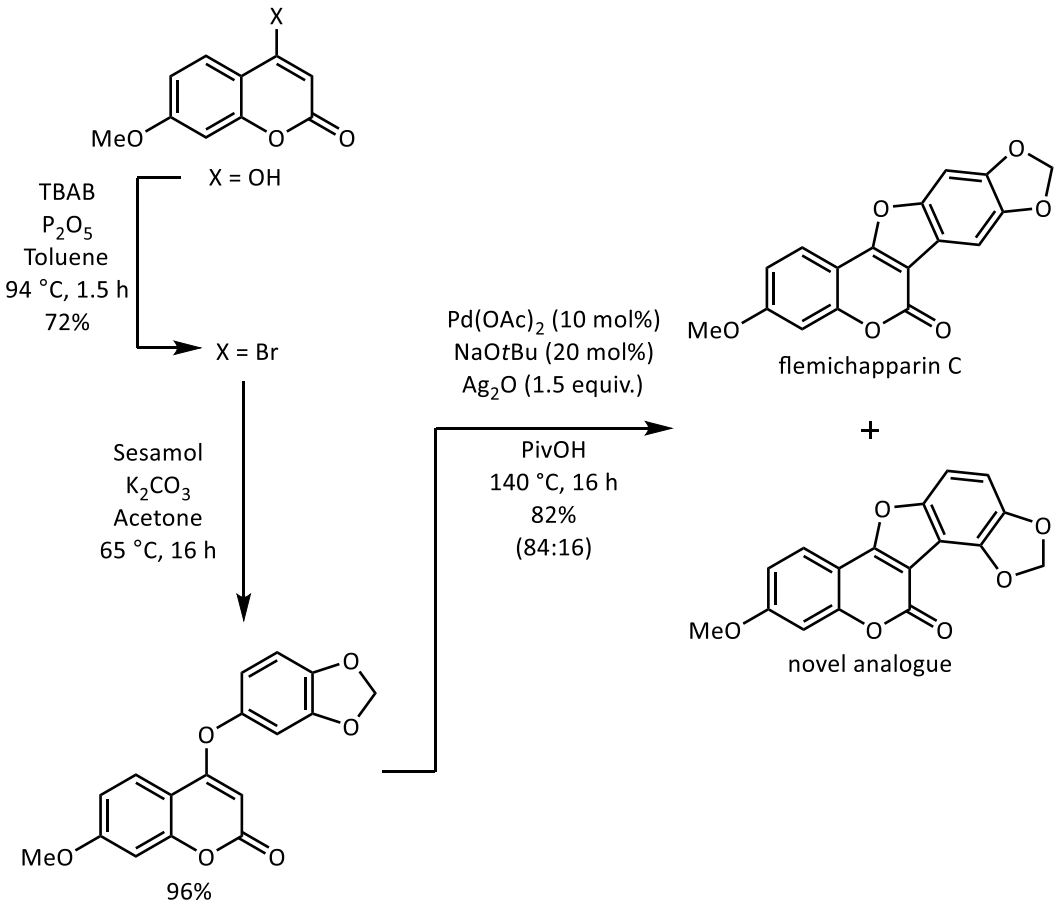


Scheme 1.32. Intramolecular direct arylation of 3-chloro-2-coumarins.

McGlacken reported the double C–H activation, or CDC, of fourteen 2-coumarin substrates (**Scheme 1.33**). The natural product flemichapparin C was synthesised as the major regioisomer in a synthetic route involving just three steps from commercially available starting materials (**Scheme 1.34**).[65] The kinetic isotope effect for the C–H activation at the C–3 position of the 2-coumarin was determined to be 1.08, showing that this was not the rate-determining step of the reaction.

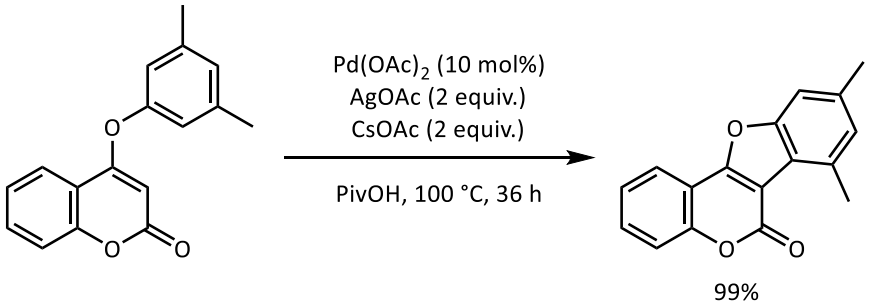


Scheme 1.33. Double C–H activation/cross-dehydrogenative coupling of 4-phenoxy-2-coumarins.



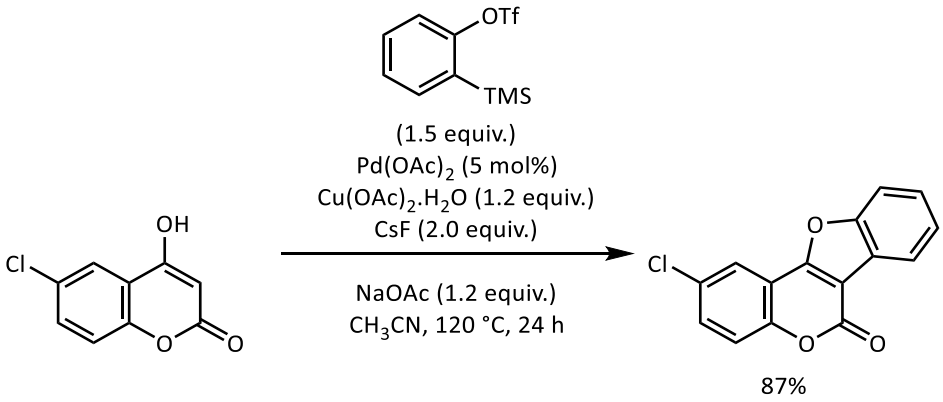
Scheme 1.34. Total synthesis of flemichapparin C in 3 steps utilising cross-dehydrogenative coupling.

Cheng *et al.* independently arrived at similar conditions for the double C–H activation of 2-coumarins (**Scheme 1.35**).[79] Synthetic routes to the natural products coumestrol and flemichapparin C using this CDC methodology were also described.



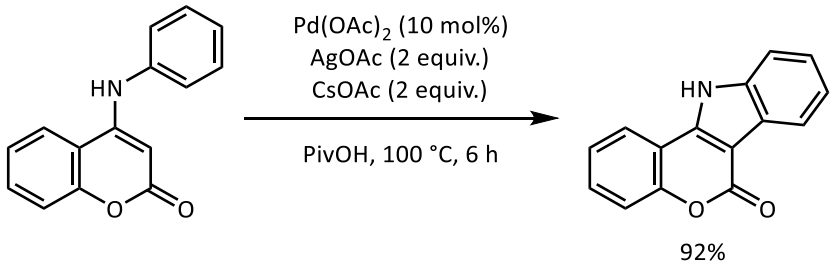
Scheme 1.35. Double C–H activation of 4-phenoxy-2-coumarins.

Gogoi and co-workers reported the direct synthesis of coumestans *via* a Pd-catalysed C–H activation/C–C and C–O bond formation cascade invoking aryne chemistry (**Scheme 1.36**).[80] Flemichapparin C was also synthesised using this methodology.



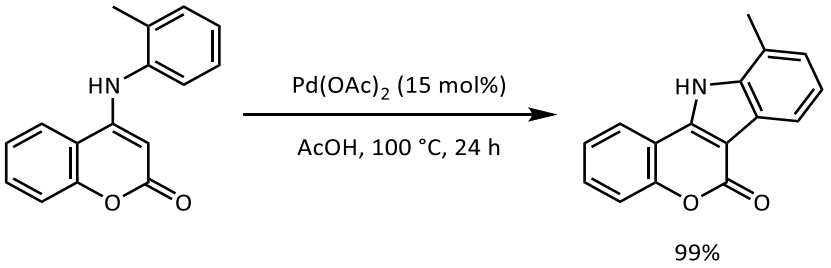
Scheme 1.36. Direct synthesis of coumestans *via* aryne chemistry.

Cheng *et al.*'s report included an expanded substrate scope involving the synthesis of indole[3,2-*c*]coumarins (**Scheme 1.37**).[79]



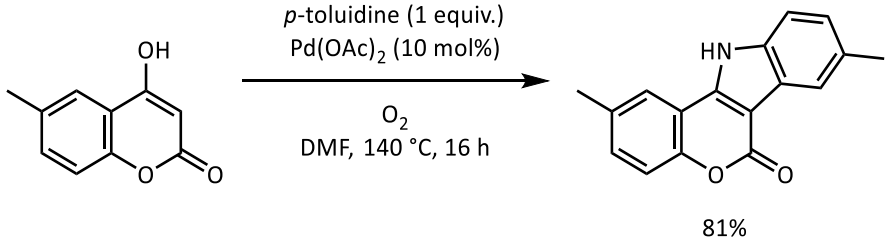
Scheme 1.37. Double C–H activation of 4-anilino-2-coumarins.

The same group subsequently reported the synthesis of indolo[3,2-*c*]coumarins from 4-aniline substituted 2-coumarins by CDC (**Scheme 1.38**) using improved conditions which did not require additional base or oxidant.[66]



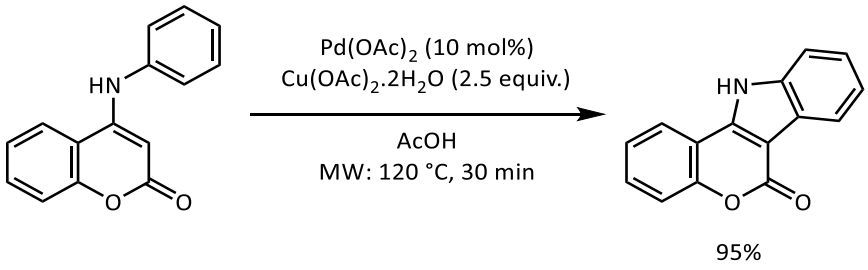
Scheme 1.38. Base-free cross-dehydrogenative coupling of 4-anilino-2-coumarins without additional oxidant.

Hajra also developed conditions for the synthesis of indolo[3,2-*c*]coumarins by CDC.[81] The synthesis of indolo[3,2-*c*]coumarins was achieved in one-pot from 4-hydroxy-2-coumarins and anilines *via* 4-anilino-2-coumarins (**Scheme 1.39**).



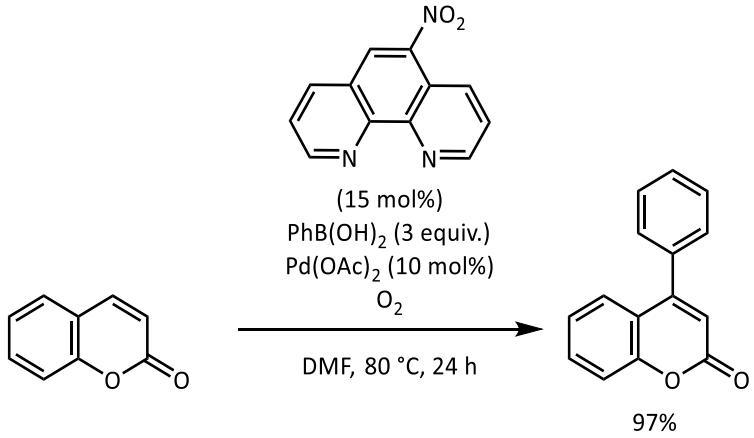
Scheme 1.39. Cross-dehydrogenative coupling of 4-anilino-2-coumarins.

Litinas published the microwave-assisted CDC of 4-anilino-2-coumarins *via* Pd-catalysis in the presence of stoichiometric $Cu(OAc)_2$ oxidant in acetic acid (**Scheme 1.40**).[82]



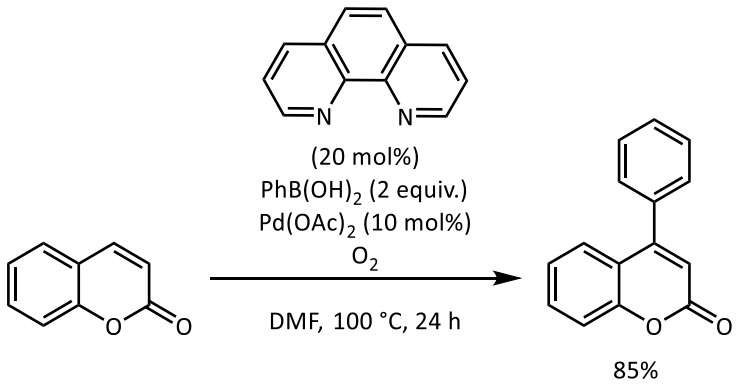
Scheme 1.40. Cross-dehydrogenative coupling of 4-anilino-2-coumarins.

An efficient protocol for the direct synthesis of 4-arylcoumarins *via* Pd-catalysed reaction of 2-coumarins and arylboronic acids was developed by Li and Duan (**Scheme 1.41**).[83] The authors describe the reaction as an oxidative Heck coupling, but no catalytic cycle was proposed.



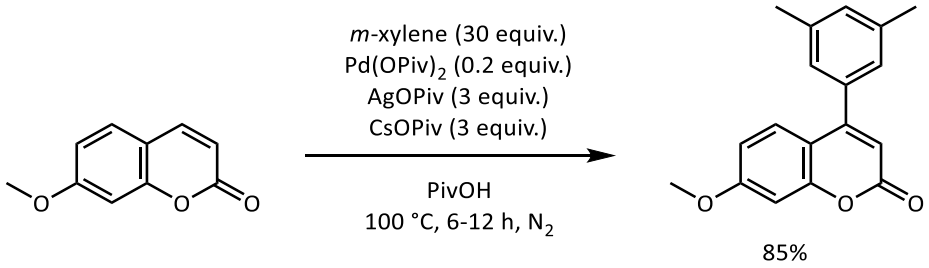
Scheme 1.41. Direct arylation of 2-coumarins.

Jafarpour and Sharfiee described a very similar regioselective intermolecular arylation of 2-coumarins *via* palladium-catalysed arylation with arylboronic acids using an unsubstituted phenanthroline ligand (**Scheme 1.42**).[84]



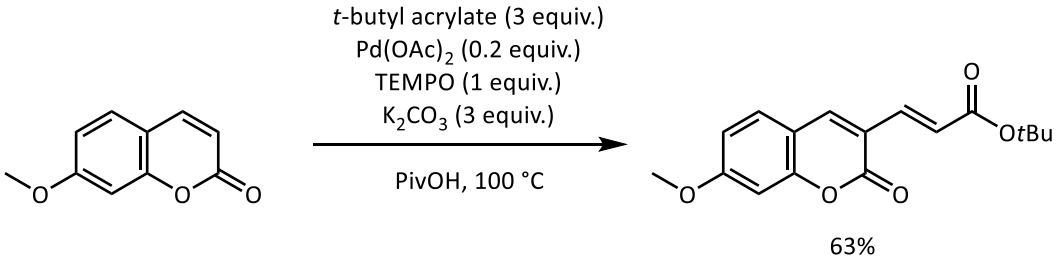
Scheme 1.42. Palladium-catalysed C–H activation of 2-coumarins.

Hong disclosed a method for the C–4 regioselective CDC of 2-coumarins with unactivated arenes, allowing the construction of 4-arylcoumarins (neoflavones) (**Scheme 1.43**).[85]

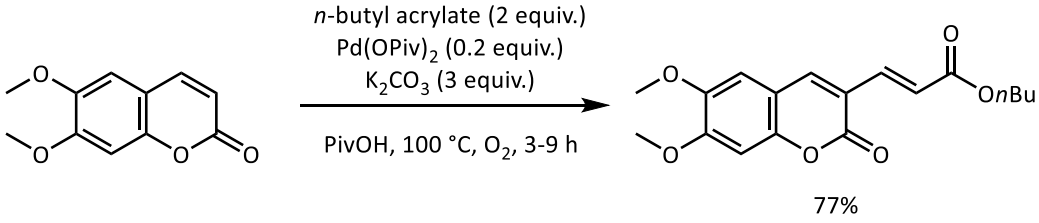


Scheme 1.43. C–4 selective cross-dehydrogenative coupling of 2-coumarins with simple arenes.

In the same report, Hong documented a preliminary direct alkenylation at C–3 of a 2-coumarin (**Scheme 1.44**).[85] This was followed by a further paper with improved conditions which did not require the radical inhibitor TEMPO (**Scheme 1.45**).[86]



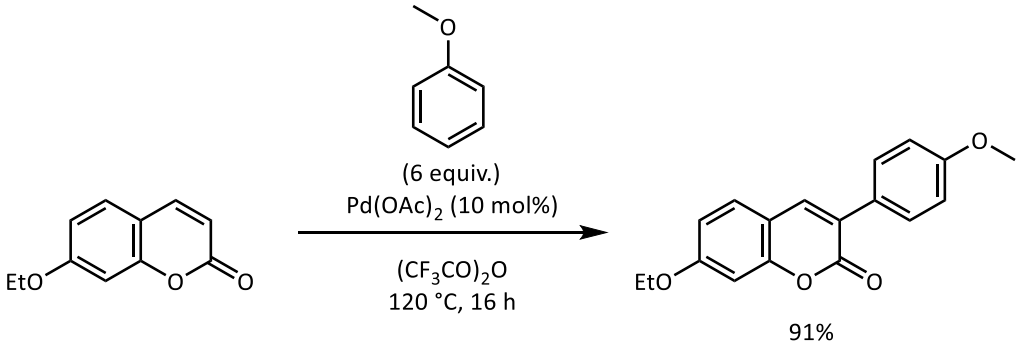
Scheme 1.44. Preliminary direct alkenylation of 2-coumarins.



Scheme 1.45. Direct alkenylation of 2-coumarins.

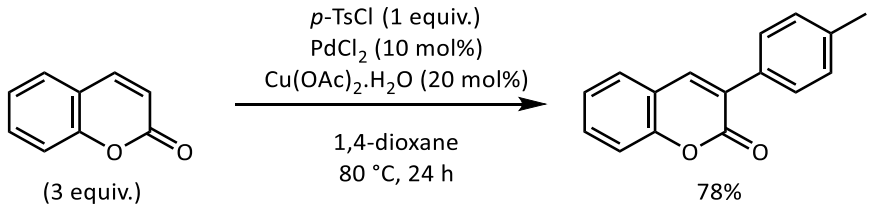
Jafarpour effected a switch in regioselectivity (**Scheme 1.46**)[87] by altering the previously reported reaction conditions shown in **Scheme 1.42**.[84] Trifluoroacetic acid anhydride (TFAA) proved an effective alternative to the sacrificial oxidant and solvent. The authors propose that $Pd(TFA)_2$ is formed from $Pd(OAc)_2$ in the presence of TFAA, and undergoes a subsequent conversion to electrophilic $Pd(OCOCF_3)^+$. Nucleophilic attack of 2-coumarin is suggested to generate a C–3 palladated intermediate, due to the more nucleophilic character of the C–3 position compared

to the C–4 position. Successive coordination with arenes, C–H bond metallation and reductive elimination releases the 3-arylcoumarin products. The authors state that the exact role of TFAA is obscured, but that it proved crucial for catalyst turnover.



Scheme 1.46. C–3 selective CDC of 2-coumarins with simple arenes.

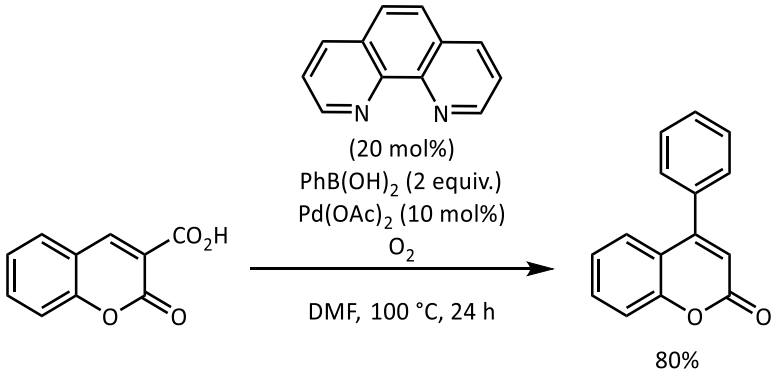
A palladium-catalysed, regioselective, direct 3-arylation of coumarins with arenesulfonyl chlorides and sodium arenesulfinates was described by Jafarpour (**Scheme 1.47**).[88] The authors propose that the first step of the mechanism is oxidative addition of Pd into the S–Cl bond of the arenesulfonyl chloride, followed by extrusion of SO_2 to generate an arylpalladium intermediate (similar to the intermediate generated from traditional oxidative addition into an arylhalide). C–H activation of the 2-coumarin, followed by successive transmetallation with the arylpalladium intermediate and reductive elimination affords the 3-arylated 2-coumarin product. The copper salt is suggested to act as an oxidant for Pd and to contribute to the desulfonation process.



Scheme 1.47. Direct arylation of 2-coumarins.

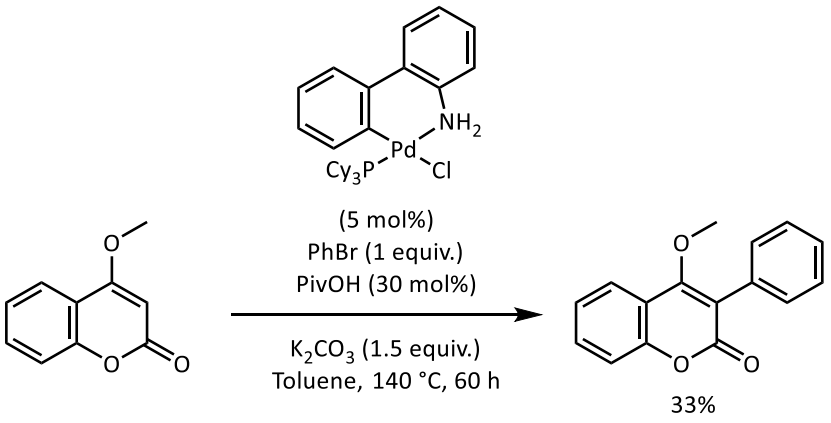
Jafarpour subsequently described the regioselective 4-arylation of 2-coumarin-3-carboxylic acids using palladium catalysis (**Scheme 1.48**).[89] The authors propose that a palladium-catalysed protodecarboxylation at C–3 is followed by a regioselective oxidative Heck reaction at C–4. When 2-coumarin-3-carboxylic acid

was submitted to the reaction conditions in the absence of arylboronic acid, the protodecarboxylated 2-coumarin was isolated in 46% yield.



Scheme 1.48. Palladium-catalysed C–H activation of coumarin-3-carboxylic acids.

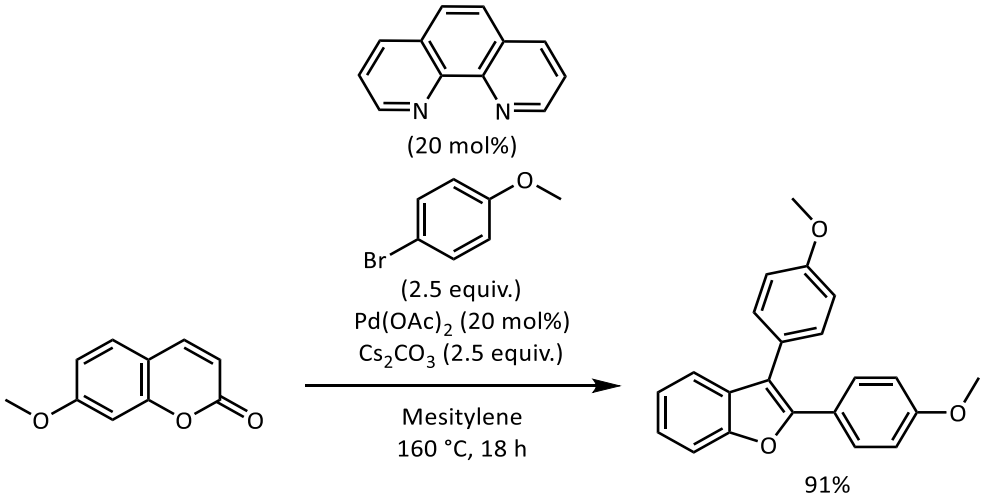
The presence of a 4-alkoxy group on the 2-coumarin framework has a dramatic effect on the relative ease of C–3–H activation and functionalisation compared to the unsubstituted 2-coumarin motif. Attempts to facilitate the intermolecular coupling of a 4-alkoxy-2-coumarin substrate by McGlacken and co-workers provided <10% yield of the desired product in all cases.[62] However, when a precatalyst (designed to produce Pd(0) quickly[29]) was utilised, the first intermolecular 3-arylation of 4-alkoxy-2-coumarins was achieved, albeit in a poor yield of 33% (**Scheme 1.49**).[62]



Scheme 1.49. Intermolecular direct arylation of 2-coumarins.

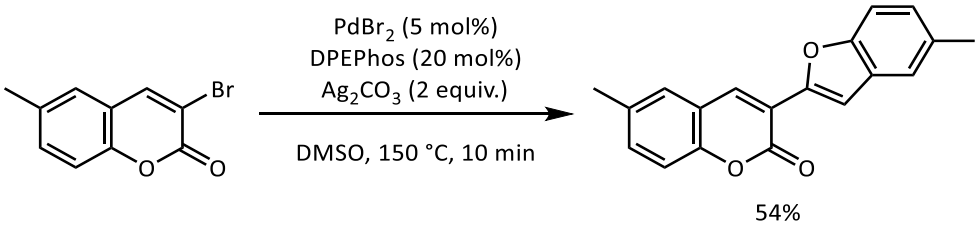
Shafiee described a protocol for the domino C–C and C–H activation of 2-coumarins.[90] A sequence of arylation-decarbonylation-arylation reactions renders 2-coumarins as convenient surrogates for the synthesis of diarylbenzo[*b*]furans (**Scheme 1.50**). The authors propose a mechanism whereby initial 3-arylation of the

2-coumarin *via* C–H activation is followed by decarbonylation of the coumarin ring with loss of CO to give a 2-arylated benzo[*b*]furan. Subsequent arylation *via* C–H activation at the 3-position of the 2-arylbenzo[*b*]furan results in the formation of the 2,3-diarylated benzo[*b*]furan.



Scheme 1.50. One-pot synthesis of benzo[*b*]furans from 2-coumarins.

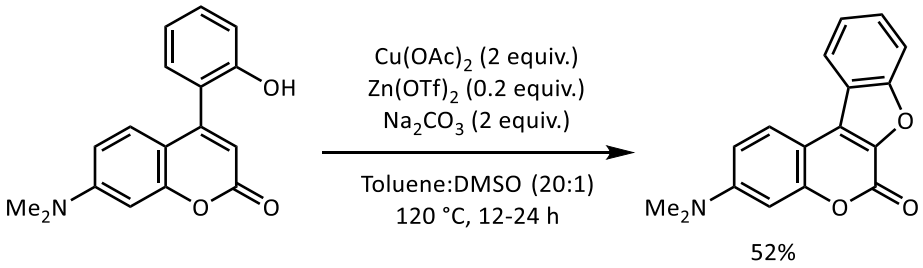
Alami and Messaoudi reported the synthesis of 3-(benzofuran-2-yl)-2-coumarins from a single starting material in one pot. This methodology involved a C–C bond formation *via* C–H activation, and C–O bond formation *via* ring contraction of 2-coumarin to 2-benzofuran under palladium catalysis (**Scheme 1.51**).[91]



Scheme 1.51. One-pot synthesis of 3-(benzofuran-2-yl)-2-coumarins.

1.6.2. Copper-mediated C–H activation

The C–O cyclisation *via* C–H functionalisation of 2-coumarins was reported by Hong (**Scheme 1.52**).[92] The C–O cyclisation of 4-arylcoumarins was possible due to the favourable metallation of the nucleophilic C–3 position.



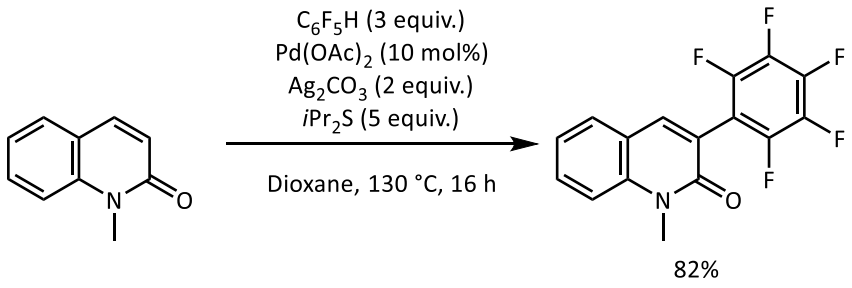
Scheme 1.52. C–O cyclisation of 4-aryl-2-coumarins.

1.7. C–H activation of 2-quinolones

2-Quinolones are structurally related to 2-pyridones, but the additional aromaticity and stability conferred by the phenyl ring on the backbone could alter the chemical reactions that this moiety participates in. As an important class of compounds, 2-quinolones are isomeric to 4-quinolones and isosteric to 2-coumarins. Compounds bearing the 2-quinolone moiety are associated with antibacterial, anticancer and antiviral properties, amongst other biological traits.[48] The 2-quinolone could potentially be more difficult to functionalise than the corresponding 2-coumarin due to the potential of the nitrogen to ligate to metal catalysts.

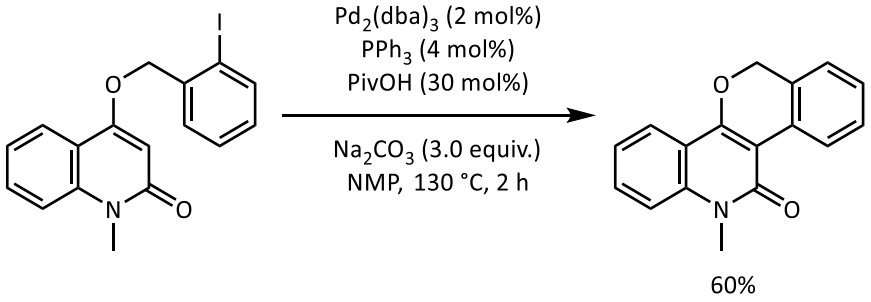
1.7.1. Palladium-catalysed C–H activation

Li described the intermolecular direct arylation of a 2-quinolone substrate (**Scheme 1.53**).[70] Pentafluorobenzene was used as a coupling partner, rendering the electron-poor aryl C–H bond more amenable to activation. Ag_2CO_3 is proposed to act as an oxidant for Pd, while *i*Pr_2S was used as an additive. The use of DMSO instead of *i*Pr_2S was reported to give a slightly lower yield. Sulfides and sulfoxides have been proposed to act as ligands to Pd which prevents the formation of palladium black.[93]



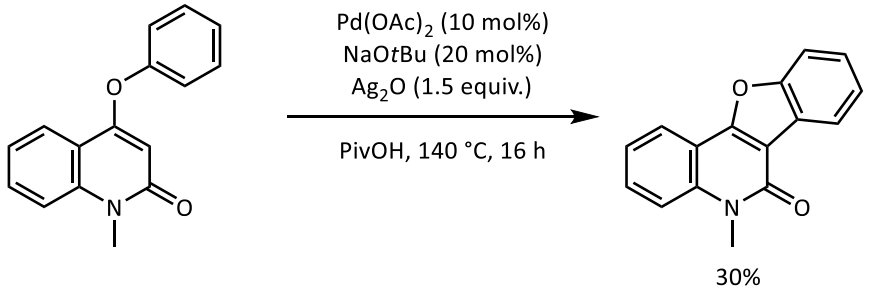
Scheme 1.53. Intermolecular cross-dehydrogenative coupling of 2-quinolones.

McGlacken reported the intramolecular direct arylation of 4-(2-iodobenzyl)oxy-2-quinolone (**Scheme 1.54**).[62] The reaction is proposed to proceed *via* a CMD mechanism.



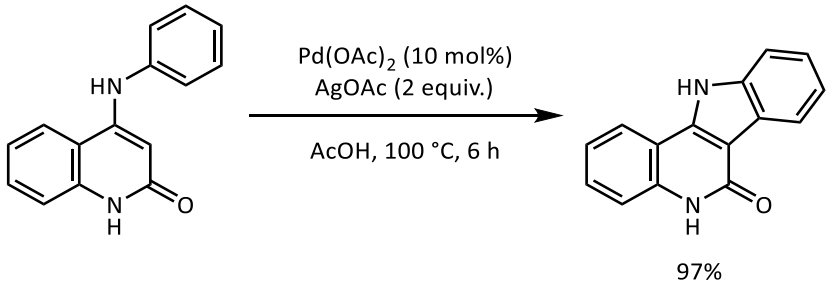
Scheme 1.54. Intramolecular direct arylation of 2-quinolones.

McGlacken described the CDC of a 4-phenoxy-2-quinolone, albeit in low yield (**Scheme 1.55**).[65]



Scheme 1.55. Cross-dehydrogenative coupling of a 2-quinolone.

Chen and Xu reported the synthesis of indolo[3,2-*c*]quinolones from 4-aniline substituted 2-quinolones by CDC (**Scheme 1.56**), expanding the scope of the base-free conditions which had been optimised for indolo[3,2-*c*]coumarins.[66]

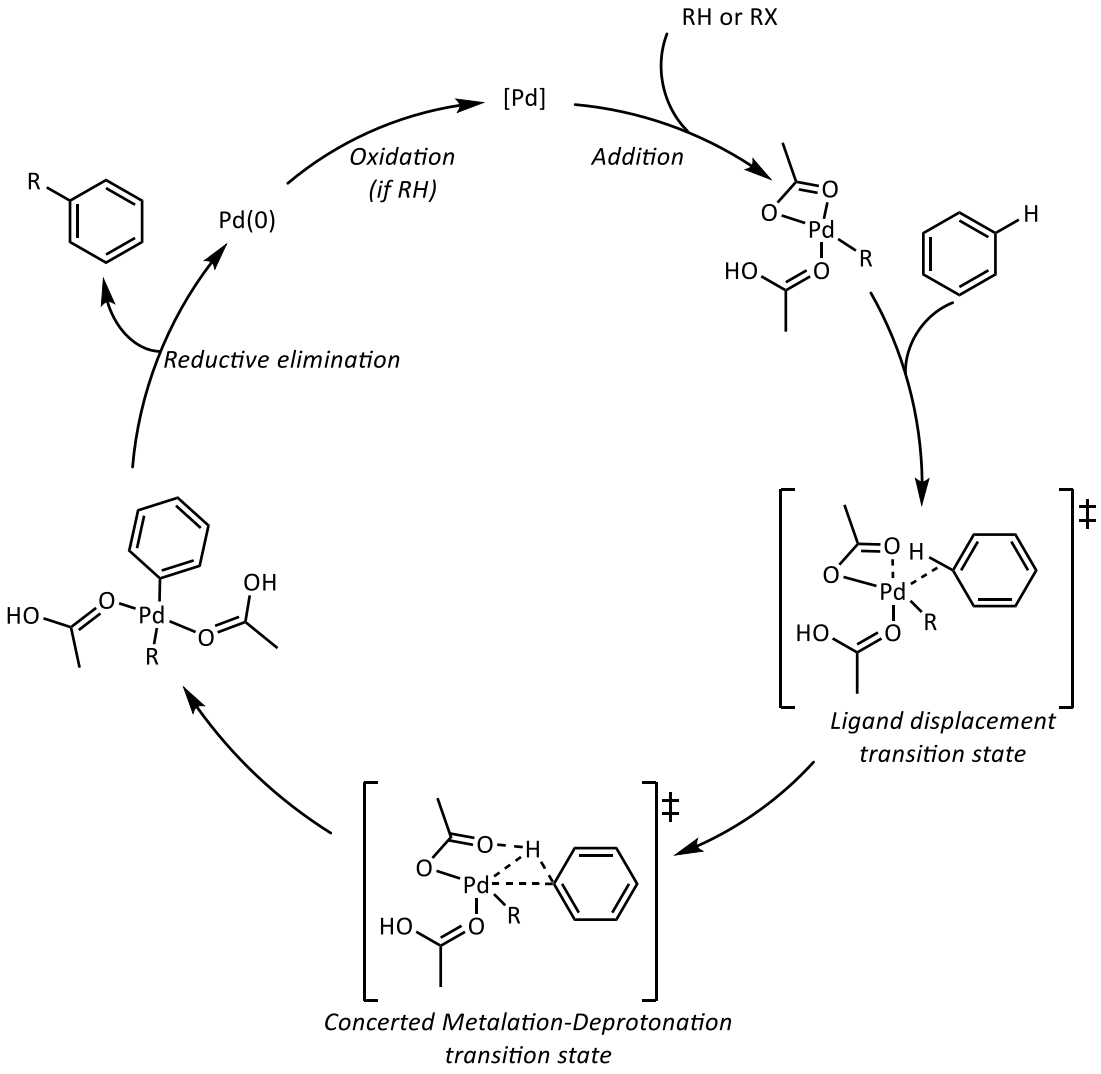


Scheme 1.56. Base-free cross-dehydrogenative coupling of 4-anilino-2-quinolones.

1.8. Mechanistic considerations

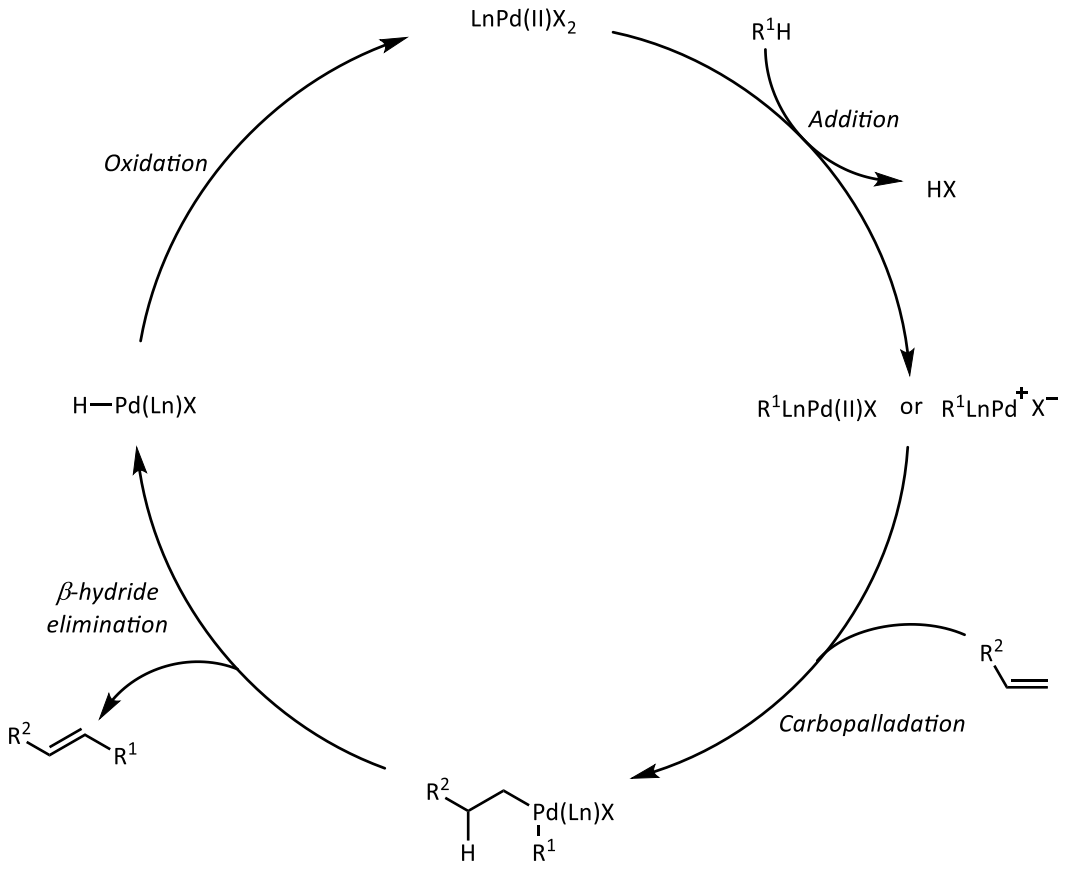
Two general mechanistic proposals dominate in these substrate classes: CMD and oxidative Heck.[94-95]

The CMD mechanism is characterised by a non-directed process whereby metallation and proton abstraction by an intramolecular carboxylate base occurs in a concerted manner (**Scheme 1.57**).[35] The first step could be oxidative addition by Pd(0) into an carbon-halide bond, or a CMD-type C–H activation of a C–H bond. A κ^2-κ^1 displacement of acetate (or other carboxylate) by the C–H bond leads to the formation of an agostic intermediate. The agostic intermediate features a polarised C–H bond that can engage in hydrogen bonding with the κ^1-OAc ligand. Cleavage of the C–H bond proceeds *via* a six-membered transition state to give a palladated intermediate. Reductive elimination of Pd(0), followed by oxidation if required, regenerates the active catalyst. Carboxylate bases possess a privileged status in this mechanism due to their chelating ability, which allows them to remain bound to the metal centre using one oxygen group, while the other effects a deprotonation.



Scheme 1.57. Generic mechanism for CMD.

On the other hand, the oxidative Heck mechanism (**Scheme 1.58**) is widely proposed to operate *via* generation of a reactive palladium species, addition of palladium to a transferable group (R^1H), coordination and insertion of the alkene (carbopalladation), Pd–H dissociation to give the product and regeneration of the active catalytic species.[95] Isomerisation of the alkene double bond may occur *via* reversible Pd–H elimination prior to release of the product.[95]



Scheme 1.58. Generic mechanistic proposal for the oxidative Heck reaction.

1.9. Conclusions and outlook

In this review, C–H activation reactions as they have been applied to 2-pyrones, 2-pyridones, 2-coumarins and 2-quinolones have been described.

Many of the C–H activation reactions reviewed here involve the 4-hydro derivatives as substrates, although 4-hydroxy and 4-alkoxy derivatives of these substrates are widely encountered in natural products. Reactions involving the 4-hydroxy moiety are particularly underdeveloped, which is remarkable considering the known potency of such compounds. The difference in reactivity observed when substitutions are made to the core 2-pyrone and 2-pyridone ring highlights that the success of reaction conditions for 4-hydro derivatives does not predicate success with the corresponding 4-hydroxy and 4-alkoxy derivatives.

The field of C–H activation in general requires more development, such that C–H bonds can be activated as required in any molecule. Although great strides have been made, a high loading of the metal catalyst (compared to traditional cross-coupling) is

often required, and necessary additives are often corrosive and/or expensive. Recent research has begun to focus on moving away from platinum group metals, towards cheaper, Earth-abundant metals[96] such as iron,[97] manganese[98] and cobalt.[99] It is also important to consider the environmental impact of new reactions. There is an increasing focus on reactions which are sustainable, particularly those executed in benign solvents.[100-101]

However, all such developments must take into consideration the eventual use of C–H activation in complex molecules with multiple functional groups. By highlighting the techniques and reaction conditions which have been used in the C–H activation of 2-pyrones and related heterocycles, it is hoped that the community will be inspired to direct their research towards milder reactions conditions. This would allow C–H activation to become a truly usable and versatile methodology which could be applied as an end-game strategy in total synthesis and the fine chemicals industry.

1.10. References

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Aims and Objectives

The overall aim of the research described in this thesis is the development of novel methodologies for the synthesis of arylated derivatives of the 2-pyrone framework, as well as the extension of any such methodology to the related 2-coumarin, 2-pyridone and 2-quinolone heterocycles.

In Chapter 2, the direct arylation of 2-pyrones, 2-pyridones and 2-coumarins *via* C–H activation will be investigated. As part of this research a number of objectives will be followed, namely:

- Develop the use of palladium to effect an intramolecular cyclisation *via* activation of the C–3–H of the 2-pyrone framework.
- Demonstrate the substrate scope through extending the optimised methodology to a range of substrates.
- Develop the use of palladium and blocking groups to effect an intramolecular cyclisation at the C–5 position of the 2-pyrone framework.
- Extend optimised synthetic methodology to a range of substrates.
- Investigate the effect of changing the nature of the intramolecular linker.
- Assess the feasibility of intermolecular direct arylation.

In Chapter 3, the Suzuki-Miyaura cross-coupling of 3-chloro-2-pyrones, 2-pyridones, 2-coumarins and 2-quinolones will be investigated. As part of this research a number of objectives will be followed, namely:

- Optimise conditions to effect the Suzuki-Miyaura cross-coupling of the 3-chloro-C–5-cyclised product of direct arylation.
- Identify a more environmentally-friendly reagent than *N*-chlorosuccinimide for chlorination of 2-pyrones and 2-coumarins.

- Develop Suzuki-Miyaura conditions for the 3-arylation of 4-alkoxy-2-coumarins in an environmentally-benign solvent.
- Identify a method to access 3-aryl-4-hydroxy-2-coumarins using protecting group chemistry.

In Chapter 4, mechanistic investigations will be performed to develop our understanding of the mechanisms through which 2-coumarins and related heterocycles undergo C–H activation and direct arylation reactions. Several objectives will be followed, namely:

- Develop protocols to introduce deuterium into target substrates.
- Conduct H–D exchange and kinetic isotope effect (KIE) experiments.
- Propose likely mechanisms for CH activation of these substrates.
- Engage with key collaborators for Density Functional Theory (DFT) calculations as required.

Chapter 2: Direct arylation of 2-pyrones and related heterocycles

…a person that started in to carry a cat home by the tail was getting knowledge that was always going to be useful to him, and warn't ever going to grow dim or doubtful.

Mark Twain

Tom Sawyer Abroad; 1894

2.1. Introduction

In this chapter the synthesis of a library of 2-pyrone, 2-pyridone and 2-coumarin compounds by direct arylation is described. It was necessary to prepare the target direct arylation substrates as they are not commercially available and several are novel.

2.2. Direct arylation at C–3

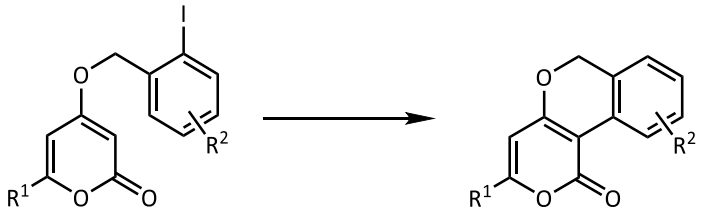
The 2-pyrone moiety represents a challenging synthon, due to its varied chemical reactivity, as described in **Chapter 1**. 2-Pyrone and its structurally related heterocycles 2-pyridone, 2-coumarin and 2-quinolone are classes of privileged biological scaffolds which display a variety of biological activity, as detailed in **Chapter 1**. Additionally, most of the direct arylation methodologies published to date have been performed on robust aryls and heterocycles, such as indoles. Consequently, the development of direct arylation methodology on the delicate 2-pyrone framework was chosen as the objective for this research because this moiety is more similar to the type of varied functionality which would be found in an active pharmaceutical ingredient or natural product.

Tricyclic 2-pyrone systems have been prepared using a catalytic C–H activation process by others.[1-3] Catalytic systems involving Pd(0) precatalysts, phosphine ligands and Cs_2CO_3 as base were employed in the formation of new five-membered rings from 4-phenoxy-2-pyrone substrates. Regioselective cyclisation at C–3 occurred. It was expected that similar methodology could be used in the formation of new six-membered rings from 4-benzyloxy-2-pyrone substrates.

2.2.1. Synthesis of substrates

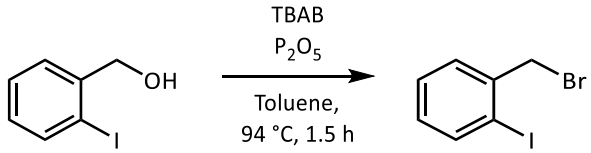
2-Pyrones

Initially, research was focused on the direct arylation of 4-benzyloxy-2-pyrones to give isochromenone-type structures *via* C–H activation (**Scheme 2.1**).



Scheme 2.1. General scheme for direct arylation of benzyloxy substrates.

For the synthesis of the target substrates, 2-iodobenzyl bromide (**2**) was required. Dihalide **2** is commercially available, but it proved more cost-effective to synthesise it in-house from 2-iodobenzyl alcohol (**1**) using standard bromination procedures. Using a procedure reported by Kato *et al.*[4] with tetrabutylammonium bromide (TBAB) as the bromide source, 2-iodobenzylbromide (**2**) was synthesised in 81% isolated yield and did not require further purification (**Scheme 2.2**).

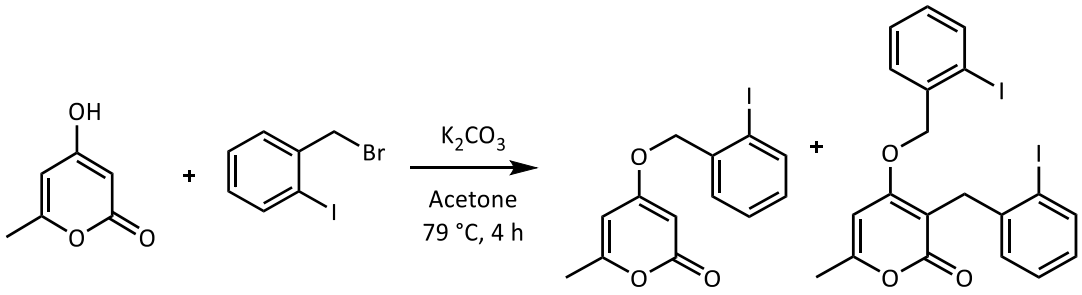


1 **2**, 81%

Scheme 2.2. Bromination of 2-iodobenzyl alcohol **1**.

The dihalide **2** was also synthesised using PBr_3 in distilled THF for 40 min, giving 75% isolated yield after recrystallisation from EtOH.[5]

4-((2-Iodobenzyl)oxy)-6-methyl-2-pyrone (**4**) was prepared from 2-iodobenzylbromide (**2**) and commercially available 4-hydroxy-6-methyl-2-pyrone (**3**) *via* a classical benzylation procedure, with **2** as the electrophile and **3** as the nucleophile (**Scheme 2.3**).[2]



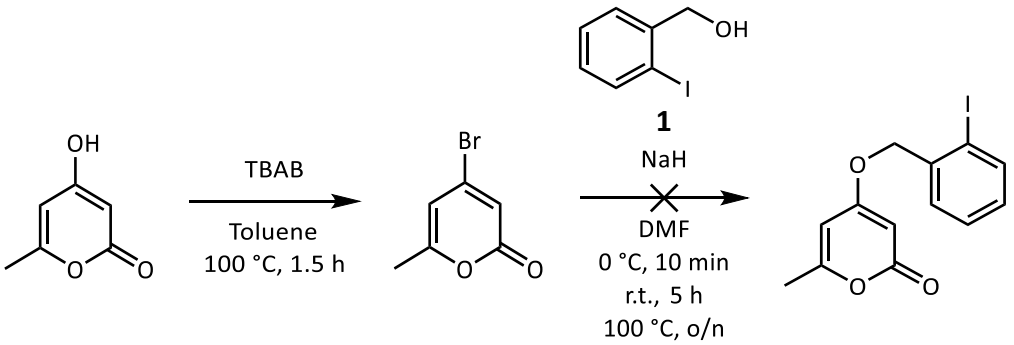
3 **2** **4**, 37% **5**, yield N. D.

crude ratio *ca.* 4:1

Scheme 2.3. Benzylation of 4-hydroxy-2-pyrone **3**.

The crude product of this reaction was purified by recrystallisation from EtOH to give **4** in 37% isolated yield. Purification of **4** by column chromatography on silica gel was found to be very low-yielding, due to the co-elution of the side product **5**, which is the product of a second benzylation at the C–3 position. A sample of **5** was isolated and the structure was determined using NMR spectroscopy and high resolution mass spectrometry.

As the purification of our desired starting material from the benzylation reaction was proving problematic, several alternative syntheses were attempted. The first involved the use of Ag_2CO_3 instead of K_2CO_3 as the base, which has been shown to promote selective *O*-alkylation in certain substrates.[6] In our case, a complex mixture of products was obtained and this method was not pursued further. Deprotonation of 2-iodobenzyl alcohol (**1**) with NaH and subsequent reaction with 4-bromo-2-pyrone **6** (prepared in 45% yield from 4-hydroxy 2-pyrone **3**) was also attempted as a regioselective route to **4**. However, even at elevated temperatures overnight, only starting materials were identified by ^{1}H NMR (**Scheme 2.4**).

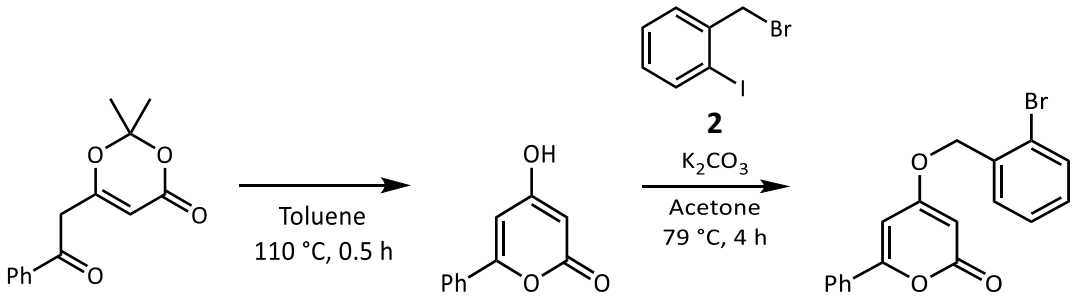


3 **6**, 45% **4**

Scheme 2.4. Attempt to promote selective O-benzylation to 2-pyrone **4**.

Since these alternative syntheses proved less successful than the original synthesis, it was determined that future preparation of **4** would use the conditions described in **Scheme 2.3**. The purification is most successful when performed on a multi-gram scale. The ratio of **4**:**5** in the crude reaction mixture was >4:1 and the desired product was isolated in 37% yield (**Scheme 2.3**). During the development of this route it was shown that bulk acetone can be used with no effect on yield, which offers an improvement over previously reported conditions.[7]

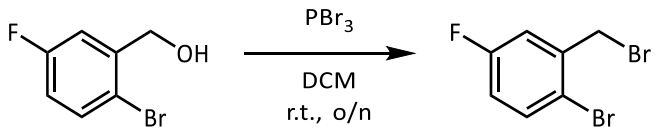
A range of C–6 substituted 2-pyrones are found in natural products.[8] Therefore, 6-phenyl-substituted 2-pyrone substrate **9** was synthesised in two steps (**Scheme 2.5**). Dioxinone **7** was heated at 110 °C in toluene for 30 min, yielding 4-hydroxy-2-pyrone **8** in 65% yield after chromatography on silica gel. The 4-hydroxy-2-pyrone **8** was then benzylated with 2-iodobenzylbromide (**2**) to yield substrate **9** in 64% yield after chromatography on silica gel. While a dibenzylation side product similar to compound **5** was observed in the ^{1}H NMR spectrum of the crude reaction mixture, it did not cause the same problems for the purification of **9**.



7 **8**, 65% **9,** 64%

Scheme 2.5. Synthesis of 4-hydroxy-6-phenyl-2-pyrone substrate **9**.

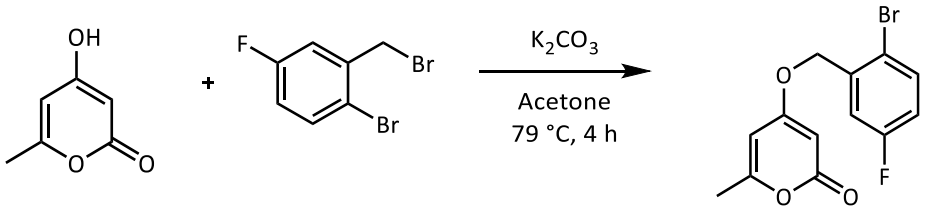
To ultimately probe the effect of electronics on the direct arylation reaction, fluorinated substrate **12** was synthesised. First, the appropriately substituted benzyl alcohol **10** was brominated to give **11** in 36% yield after column chromatography on silica gel (**Scheme 2.6**).



10 **11**, 36%

Scheme 2.6. Synthesis of 5-fluoro-2-iodobenzylbromide (**11**).

Compound **11** was then reacted with 2-pyrone **3** in the presence of K_2CO_3 to give **12** in 45% yield after chromatography on silica gel (**Scheme 2.7**). While a dibenzylation side product similar to compound **5** was observed in the ^{1}H NMR spectrum of the crude reaction mixture, it did not cause the same problems for the purification of **12**.

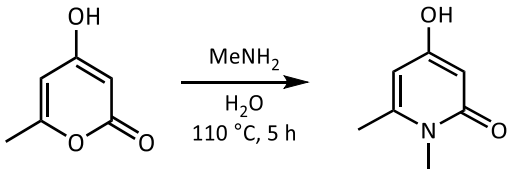


3 **11** **12** 45%

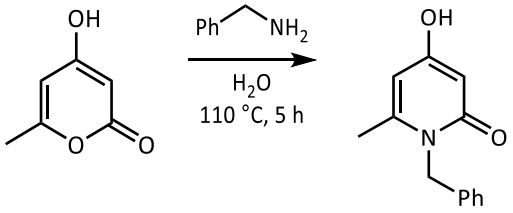
Scheme 2.7. Synthesis of aryl substituted 2-pyrone **12**.

2-Pyridones

2-Pyridone compounds are potential bioisosteres of 2-pyrone compounds, and have also been demonstrated to possess impressive biological activity.[9-10] 4-Hydroxy-1,6-dimethylpyridin-2(1*H*)-one (**13**) and 1-benzyl-4-hydroxy-6-methylpyridin-2(1*H*)-one (**14**) were synthesised from 4-hydroxy-6-methyl-2-pyrone (**3**) in refluxing water (**Scheme 2.8**), and isolated in 50% and 51% yield respectively. Characterisation data corresponded to that reported in the literature.[11-12]



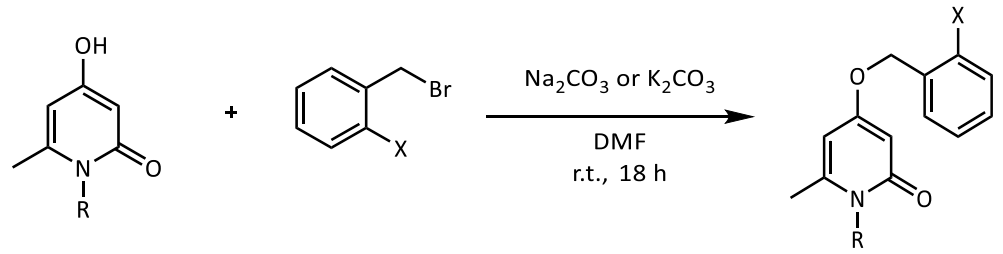
3 **13**, 50%



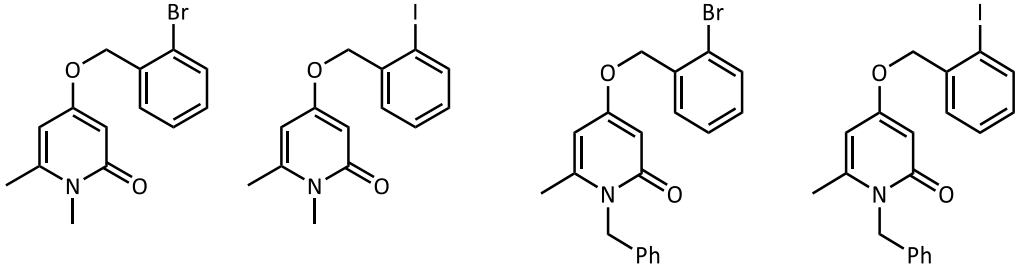
3 **14**, 51%

Scheme 2.8. Synthesis of substituted 2-pyridones **13**-**14**.

Once synthesised, the substituted 2-pyridone compounds were benzylated using the reported procedure.[13] The complete separation of mono- and di-benzylated compounds was achieved using column chromatography on silica gel with EtOAc/hexanes as the eluent. Both the bromo- and iodo- analogues were prepared (**Scheme 2.9**) to examine if the halide had an effect on the final direct arylation of the substituted 2-pyridone compounds.



13-**14** X = I (**2**), Br **15**-**18**

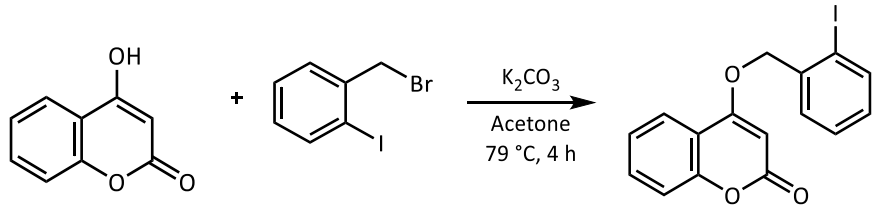


15, 70% from **13** **16**, 29% from **13** **17**, 53% from **14** **18**, 55% from **14**

Scheme 2.9. Synthesis of 4-benzyloxy 2-pyridones **15**-**18**.

2-Coumarins

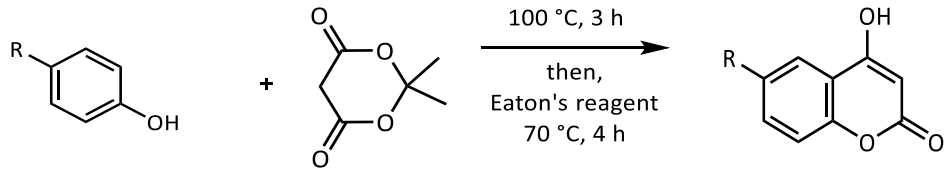
2-Coumarin compounds are structurally related to the 2-pyrone compounds, and have also been demonstrated to possess interesting bioactivity.[14] 4-Hydroxy-2-coumarin (**19**) is commercially available and was benzylated using the procedure shown in **Scheme 2.10**.



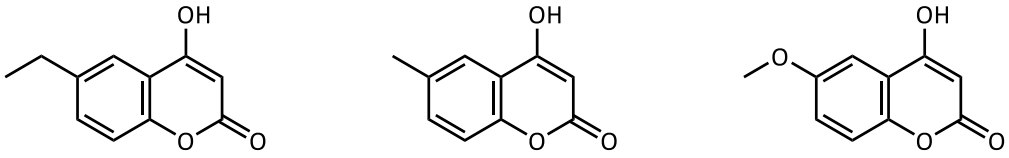
19 **2** **20**, 45%

Scheme 2.10. Benzylation of 4-hydroxy-2-coumarin (**19**).

6-Ethyl-4-hydroxy-2-coumarin (**21**), 6-methyl-4-hydroxy-2-coumarin (**22**) and 6-methoxy-4-hydroxy-2-coumarin (**23**) were synthesised using a one-pot procedure reported by Gao *et al*.[15] Starting from the corresponding phenol and Meldrum's acid, the target coumarins were isolated in good yields after recrystallisation of the crude product from EtOH (**Scheme 2.11**).



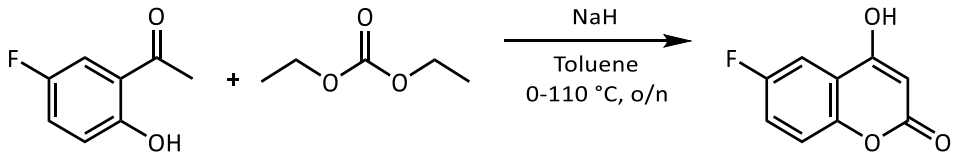
21-**23**



21, 76% **22**, 71% **23**, 31%

Scheme 2.11. Synthesis of substituted 4-hydroxy-2-coumarins **21**-**23**.

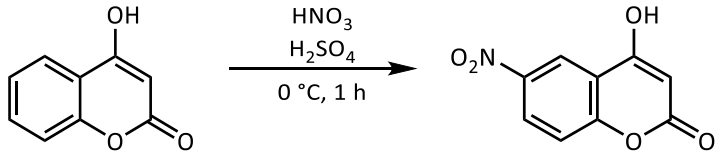
For 2-coumarins bearing electron-withdrawing groups, an alternative synthesis was required.[16-17] 5-Fluoro-2-hydroxyacetophenone was reacted with diethyl carbonate in the presence of NaH to give 6-fluoro-4-hydroxy-2-coumarin (**24**) in 26% yield after recrystallisation from EtOH (**Scheme 2.12**).



24, 26%

Scheme 2.12. Synthesis of 6-fluoro-4-hydroxy-2-coumarin (**24**).

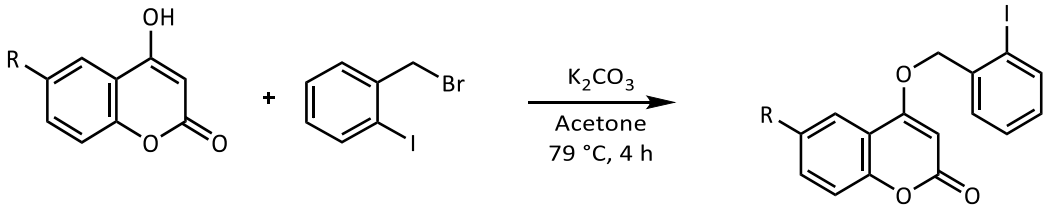
6-Nitro-4-hydroxy-2-coumarin (**25**) was synthesised by nitration of 4-hydroxy-2-coumarin (**19**) (**Scheme 2.13**).[18] The ^{1}H NMR spectrum of the crude reaction mixture showed residual starting material **19** and the selectively 6-nitrated product **25**, which was isolated, albeit in a poor yield of 26%, after recrystallisation from EtOH.



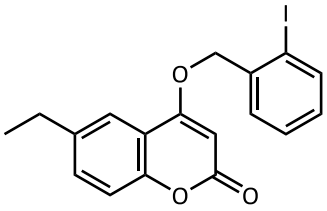
19 **25**, 26%

Scheme 2.13. Nitration of 4-hydroxy-2-coumarin (**19**).

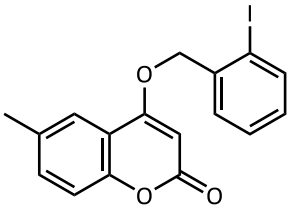
The 4-hydroxy-2-coumarins **21**-**25** were then benzylated using 2-iodobenzylbromide (**2**) and purified by column chromatography on silica gel using DCM:MeOH as eluent to give **26**-**30** in moderate yields (**Scheme 2.14**).



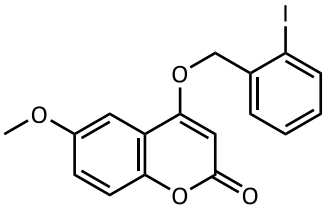
21-**25** **2** **26**-**30**



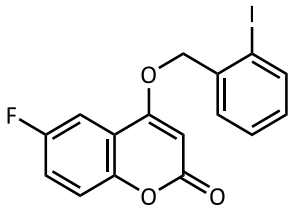
26, 42% from **21**



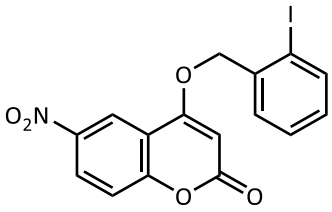
27, 42% from **22**



28, 20% from **23**



29, 52% from **24**

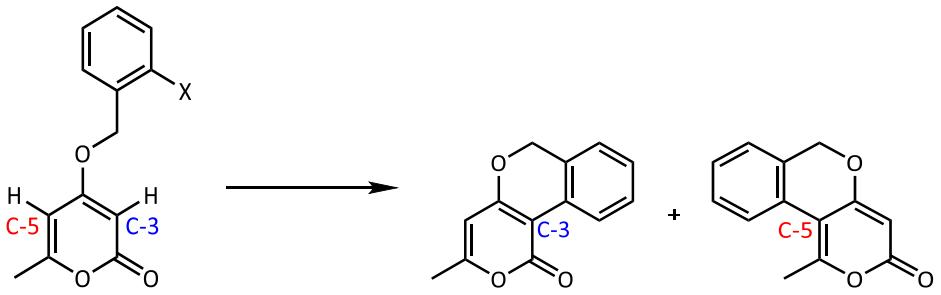


30, 50% from **25**

Scheme 2.14. Benzylation of substituted 4-hydroxy-2-coumarins **21**-**25**.

2.2.2. Optimisation of reaction conditions for C–3 arylation

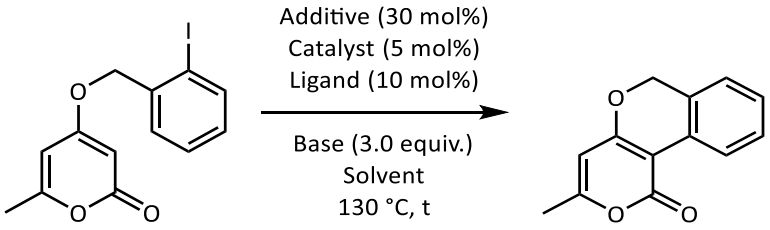
With the desired substrates in hand, the development of reaction conditions to effect the direct arylation *via* C–H activation began. It was anticipated that both C–3 and C–5 cyclisation could occur (**Scheme 2.15**).



Scheme 2.15. Direct arylation of 4-benzyloxy 2-pyrones with two potential C–H activation sites.

The Pd-catalysed cyclisation of 2-pyrones to form five-membered rings has been reported by Fairlamb.[3] However, the reported conditions gave poor conversion to six-membered rings in our hands (**Table 2.1**, **entry 1**). Previously reported cyclisations by Majumdar[1-2] and the McGlacken group to give six-membered rings,[7] using so-called Jeffery's conditions,[19] required the use of stoichiometric or superstoichiometric amounts of TBAB and thus suffer from poor atom and cost economy, and falter from an environmental viewpoint.

Table 2.1. Optimisation of direct arylation conditions.



4 **31**

Entry	Additive	Catalyst	Ligand	Base	Solvent	Time (h)	Yield (%)[a]
1	–	$Pd_2(dba)_3$	PPh_3	Na_2CO_3	NMP	2	11
2	PivOH	$Pd_2(dba)_3$	PPh_3	Na_2CO_3	NMP	2	(77)
3	TFA	$Pd_2(dba)_3$	PPh_3	Na_2CO_3	NMP	18	7
4	Butyric acid	$Pd_2(dba)_3$	PPh_3	Na_2CO_3	NMP	18	6
5	Acetic acid	$Pd_2(dba)_3$	PPh_3	Na_2CO_3	NMP	18	5
6	Isobutyric acid	$Pd_2(dba)_3$	PPh_3	Na_2CO_3	NMP	18	13
7	Citric acid	$Pd_2(dba)_3$	PPh_3	Na_2CO_3	NMP	18	9
8	Ph_2CHCO_2H	$Pd_2(dba)_3$	PPh_3	Na_2CO_3	NMP	18	13
9	1-adamantoic acid	$Pd_2(dba)_3$	PPh_3	Na_2CO_3	NMP	2	(62)
10	PivOH	$Pd(OAc)_2$	PPh_3	Na_2CO_3	NMP	2	64 (54)
11	PivOH	$Pd(dba)_2$	PPh_3	Na_2CO_3	NMP	2	51
12	PivOH	$Pd(PPh_3)_4$	PPh_3	Na_2CO_3	NMP	2	66
13	PivOH	$Pd_2(dba)_3$	DavePhos	Na_2CO_3	NMP	2	48
14	PivOH	$Pd_2(dba)_3$	cataCXium®A	Na_2CO_3	NMP	2	52
15	PivOH	$Pd_2(dba)_3$	$PCy_3.HBF_4$	Na_2CO_3	NMP	2	60
16	PivOH	$Pd_2(dba)_3$	PPh_3	K_2CO_3	NMP	2	42 (38)
17	PivOH	$Pd_2(dba)_3$	PPh_3	NaOAc	NMP	2	70
18	PivOH	$Pd_2(dba)_3$	PPh_3	Na_2CO_3	DMA	2	56 (30)
19	PivOH	$Pd_2(dba)_3$	PPh_3	Na_2CO_3	Toluene	2	7

[a]Yields determined from the ^1H NMR spectrum of the crude reaction mixture with 1,3,5-trimethoxybenzene as the internal standard for quantification. Isolated yields in parentheses.

The addition of an acidic co-catalyst, pivalic acid (PivOH), greatly enhanced the efficiency of the reaction, and the desired product **31** was obtained in 77% isolated yield (**Table 2.1**, **entry 2**). Fagnou demonstrated that PivOH is a promoter of the CMD reaction pathway for C–H activation,[20] which had previously been described by Echavarren[21-22] and Davies/Macgregor.[23-24] Interestingly, Fairlamb reported that the addition of PivOH to their system for the direct arylation of 4-phenoxy-2-pyrones to give five-membered rings led to a reduction in yield from 79% to 45%.[3] This is an indication that a different mechanism could be at play in the 4-benzyloxy system compared to Fairlamb's 4-phenoxy system. Mechanistic insights into the 4-benzyloxy system will be further discussed in **Chapter 4**.

An extensive screen of other acidic co-catalysts was then undertaken (**Table 2.1**, **entries 3-9**). Acids with a pK_a similar to that of PivOH (**Table 2.1**, **entry 2**) such as acetic acid (**Table 2.1**, **entry 5**) and isobutyric acid (**Table 2.1**, **entry 6**) resulted in incomplete consumption of the starting material. Of the eight acids tested, PivOH (**Table 2.1**, **entry 2**) and 1-adamantoic acid (**Table 2.1**, **entry 9**) gave complete consumption of starting material, and in only 2 h. Given the higher yield with PivOH compared to 1-adamantoic acid, this additive was used in the optimisation of the other components of the reaction (**Table 2.1**, **entries 10-19**). Of the palladium catalysts screened, only $Pd(OAc)_2$ (**Table 2.1**, **entry 10**) and $Pd_2(dba)_3$ (**Table 2.1**, **entry 2**) facilitated complete consumption of starting material. Other phosphine ligands, such as DavePhos (**Table 2.1**, **entry 13**), cataCXium®A (**Table 2.1**, **entry 14**) and $PCy_3.HBF_4$ (**Table 2.1**, **entry 15**) did not perform as well as PPh_3 (**Table 2.1**, **entry 2**). Carbonate bases are typically used in direct arylation reactions involving PivOH as a co-catalyst.[24] K_2CO_3 (**Table 2.1**, **entry 16**) gave a reduced yield compared to Na_2CO_3. It is possible that the stronger base caused degradation of the 2-pyrone motif. NaOAc gave a moderate yield (**Table 2.1**, **entry 17**), and Na_2CO_3 remained the preferred base in this system. The reaction proceeded to completion in DMA, but with a reduced yield (**Table 2.1**, **entry 18**). Polar aprotic solvents are generally the solvents of choice for direct arylation reactions involving palladium catalysts, so it is unsurprising that toluene gave a very poor yield of 7% (**Table 2.1**, **entry 19**). NMP was favoured as the reaction solvent as it gave the best yield (**Table 2.1**, **entry 2**).

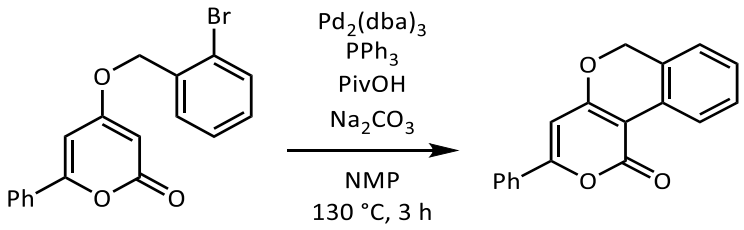
It was found by another member of the McGlacken group[25] that reducing the palladium loading to 2 mol% with a concomitant reduction of PPh_3 to 4 mol% resulted in no reduction in yield.[26] McGlacken and co-workers have previously shown that lower catalytic loadings of palladium can have a positive outcome on reaction efficiency.[7] The optimal conditions for direct arylation to give product **31** involved $Pd_2(dba)_3$ (2 mol%), PPh_3 (4 mol%), PivOH (30 mol%) and Na_2CO_3 (3 equiv.) in NMP at 130 °C for 2 h.

The C–3 arylated product **31** was strongly favoured in all cases shown in **Table 2.1**. The C–5 arylated product **32** was observed in the ^{1}H NMR spectrum of the crude reaction mixture for reactions involving 6-methyl-2-pyrones and the related product was observed for 6-methyl-2-pyridones. However, complete regioselectivity was observed with other C–6-substituted 2-pyrones, as in **Scheme 2.16**. Complete consumption of starting material **4** was achieved at the lower temperature of 100 °C in 5 h, with all other parameters the same as the optimal conditions. However, an erosion of yield and regioselectivity was observed. There was a 78:22 ratio of **31**:**32** determined from the ^{1}H NMR spectrum of the crude reaction mixture, and product **31** was isolated in 46% yield.

2.2.3. Demonstration of substrate scope for C–3 arylation

With the optimised conditions in hand, the broader applicability of the system was tested using the previously synthesised library of compounds.

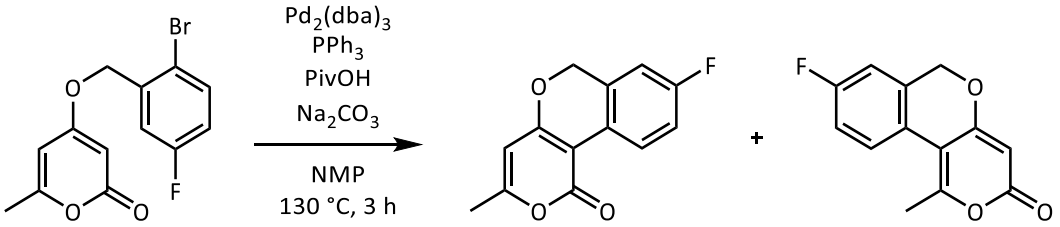
It is generally accepted that oxidative addition occurs faster into C–I bonds compared to C–Br bonds.[27] Interestingly, using the aryl bromide **9** in the conditions optimised for an aryl iodide did not seem to have an appreciable effect on yield or reaction time. The product **33** was isolated in 61% yield after chromatography on silica gel. In this case, complete regioselectivity was observed for C–3 arylation, presumably due to the steric influence of the phenyl group making the C–5 site disfavoured (**Scheme 2.16**).



9 **33**, 61%

Scheme 2.16. Direct arylation of 6-phenyl-2-pyrone **9**.

To determine the effect of placing an electron-withdrawing group *para* to the site of oxidative addition, 2-pyrone **12** was subjected to the reaction conditions (**Scheme 2.17**).



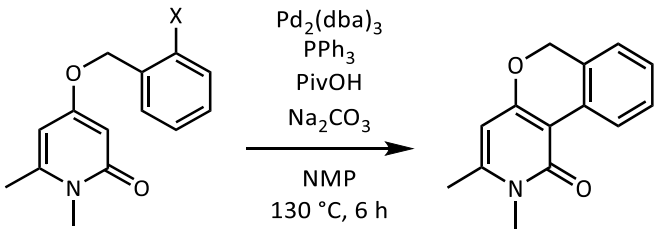
12 **34**, 65% **35**, 15%

Scheme 2.17. Direct arylation of a 2-pyrone **12** with substituted aryl group.

The presence of the *p*-fluoro group had a significant effect on the reaction, and the C–5 arylated product **35** was formed as a side-product in isolable quantities for the first time using these conditions. Previously, only trace quantities of the C–5 arylated product could be observed in the ^{1}H NMR spectrum of the crude reaction mixture from **4** using the PivOH conditions. The reason for the decline in regioselectivity is attributed to an increase in reactivity, especially considering the poor yield using an electron-rich *p*-methoxy substrate.[26] Electron-poor aryl halides oxidatively add to Pd(0) more readily than the corresponding electron-rich aryl halides.[28] This could lead to the oxidative addition product of electron-rich aryl halides persisting for longer, and ultimately, lead to degradation of the oxidative addition product.

The substituted 2-pyridones **15**-**18** were subjected to the optimised direct arylation conditions (**Scheme 2.18**). Complete consumption of starting material took longer (6 h) for the 2-pyridone substrates compared to the 2-pyrone (2 h). The use of an iodide instead of a bromide is necessary to achieve good yields for these substrates.

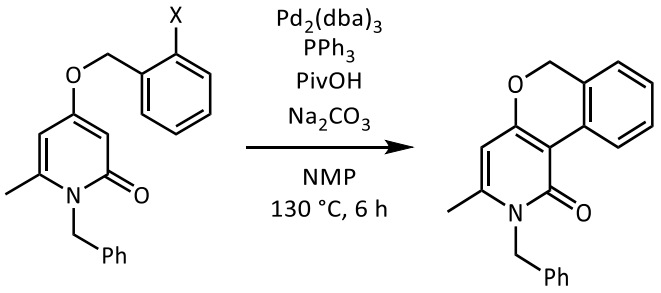
This may be due, in part, to faster oxidative addition of the Pd(0) species into the C–I bond *versus* the C–Br bond.[27] It was anticipated that the nitrogen of the 2-pyridone, particularly the 2-pyridone bearing a free N–H bond,[25-26] could ligate to Pd and hinder the reaction, but pleasingly, these substrates were well tolerated.



36

15 X = Br 26% from **15**

16 X = I 74% from **16**



37

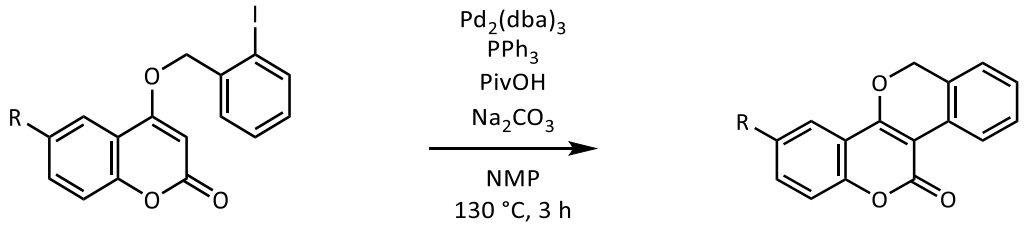
17 X = Br 42% from **17**

18 X = I 77% from **18**

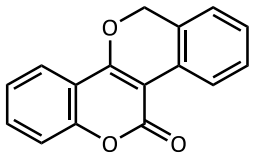
Scheme 2.18. Direct arylation of 2-pyridones **15**-**18**.

2-Coumarin substrates were also subjected to the direct arylation conditions (**Scheme 2.19**). Using 4-((2-iodobenzyl)oxy)-2-coumarin (**20**) facilitated smooth coupling and the reaction furnished **38** in 61% yield. A short substrate scope involving substitution of the 2-coumarin aryl ring was investigated and good yields were observed for electron-rich 2-coumarins affording **39**-**41**. These yields were broadly in line with those observed for the 2-pyrone and 2-pyridone substrates, showing that the additional aromaticity conferred by the aryl ring of the 2-coumarin did not have a perceptible effect on the outcome of the reaction. A slight reduction in yield was observed for electron-poor 2-coumarins with the 6-fluoro **42** and 6-nitro **43** products

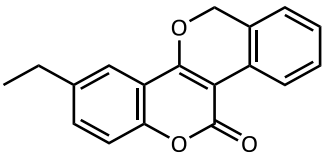
formed in 43% and 58% yields respectively. These electronic effects will be further discussed in **Chapter 4**.



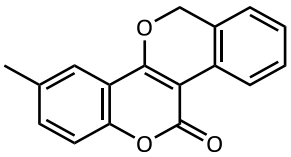
20, **26**-**30** **38**-**43**



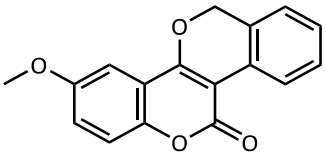
38, 61% from **20**



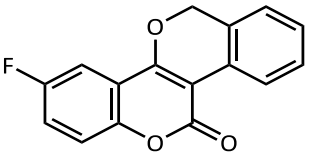
39, 71% from **26**



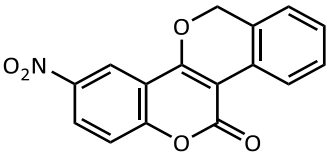
40, 71% from **27**



41, 82% from **28**



42, 43% from **29**

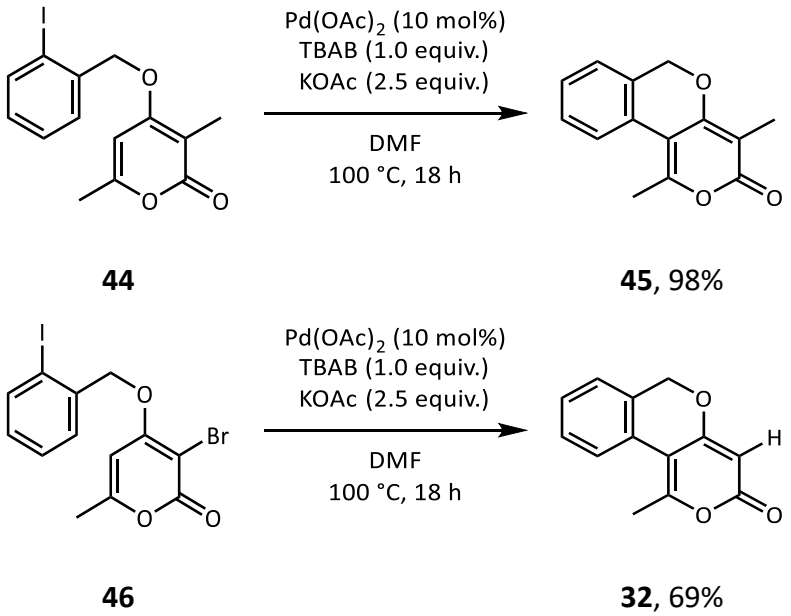


43, 58% from **30**

Scheme 2.19. Direct arylation of 2-coumarins **20**, **26**-**30**.

2.3. Direct arylation at C–5

As previously discussed, the 2-pyrone framework bears two potential sites for C–H activation. The C–3 site has shown preferential reactivity towards C–H activation compared to the C–5 site. However, previous work by McGlacken and co-workers demonstrated that when the C–3 site is blocked, C–5 arylation occurs in excellent yields (**Scheme 2.20**).[7]



Scheme 2.20. Blocking groups for C–5 arylation.

The Fairlamb group[29] installed a methyl group in the 3-position to give substrate **44**. The direct arylation reaction proceeded to give **45** in an excellent yield of 98%. However, the methyl group is not a useful blocking group as it cannot be easily removed or further functionalised. It was reasoned that using a bromide blocking group at C–3 could allow the direct arylation to proceed. Additionally, retention of the C–Br bond would provide a synthetic handle for further cross-coupling, provided oxidative addition was preferred at the aryl iodide and no complications were encountered due to the C–Br bond at C–3. Direct arylation of **46** was accomplished within the McGlacken group, however, product hydrodebromination also occurred to give **32**.[7] All attempts by other members of the McGlacken group to expand the substrate scope of this direct arylation/hydrodebromination reaction to 2-pyridones were unsuccessful.[25] While selective C–5 cyclisation was achieved using methyl and bromide blocking groups, gaining access to 5-cyclised compounds bearing a halogen

at C–3 would require the re-installation of a halide, which would be neither atom- nor step-economic.

2.3.1. Synthesis of substrates

2-Pyrones

Cyclisation at the C–5 position of 2-pyrones gives access to an untapped heterocyclic framework, opening up new opportunities for the synthesis of valuable analogues not currently accessible by traditional synthetic methodologies (**Figure 2.1**).

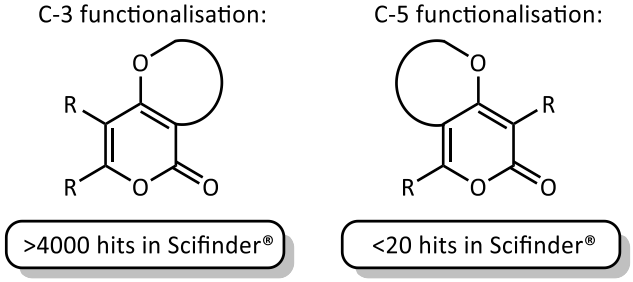


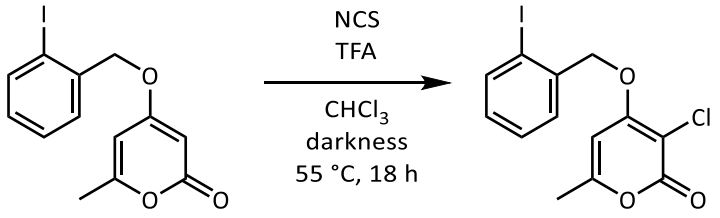
Figure 2.1. Untapped biological potential of C–5 cyclised 2-pyrones.

We sought to develop a Pd-catalysed direct arylation protocol which would:

1. Give direct arylation at C–5.
2. Be more generally applicable.
3. Allow further decoration of the 2-pyrone motif at C–3.

As Lautens observed,[30] there is a notable absence of polyhalogenated substrates in Pd-catalysed cross-coupling, which is probably due to selectivity issues. This potential pitfall was offset by the potential for follow-on coupling using a (hetero)aryl chloride, the benefits of which have been well documented by Buchwald,[31-34] Hartwig[35-37] and Fu.[38-42] Fu stated that *"aryl chlorides are both more readily available and less expensive than aryl bromides and aryl iodides"*.[38] *"From a practical point of view, the use of aryl chlorides is highly desirable… However, they are much more difficult to activate than aryl iodides and bromides*" according to Jin.[43]

It was therefore decided to install a 3–Cl blocking group, giving substrate **47**, which should be stable towards the oxidative conditions of the direct arylation reaction, yet reactive enough to allow further decoration of the 2-pyrone framework using cross-coupling methods applicable to aryl chlorides. Chlorination of 2-pyrone **4** was achieved with NCS in the presence of TFA to give **47** in 65% yield (**Scheme 2.21**).

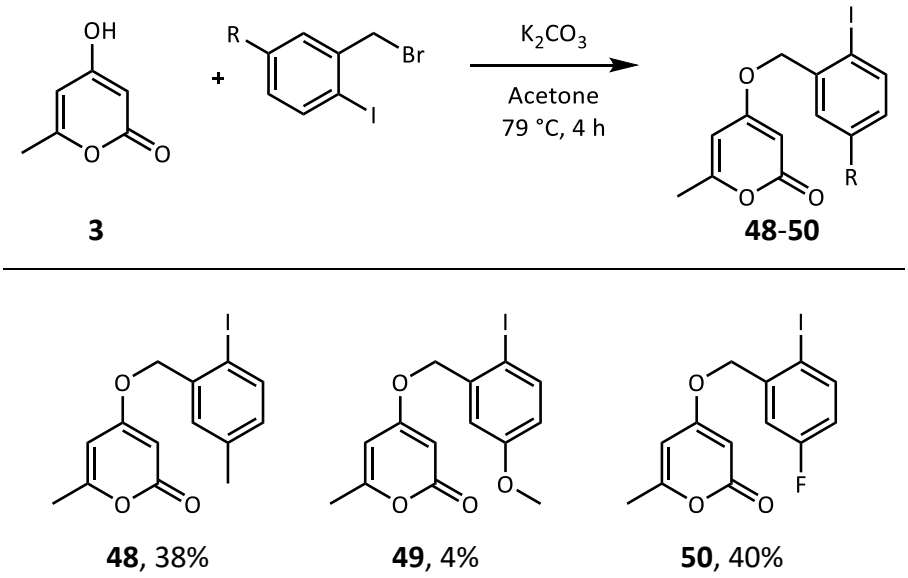


4 **47**, 65%

Scheme 2.21. Chlorination of **4**.

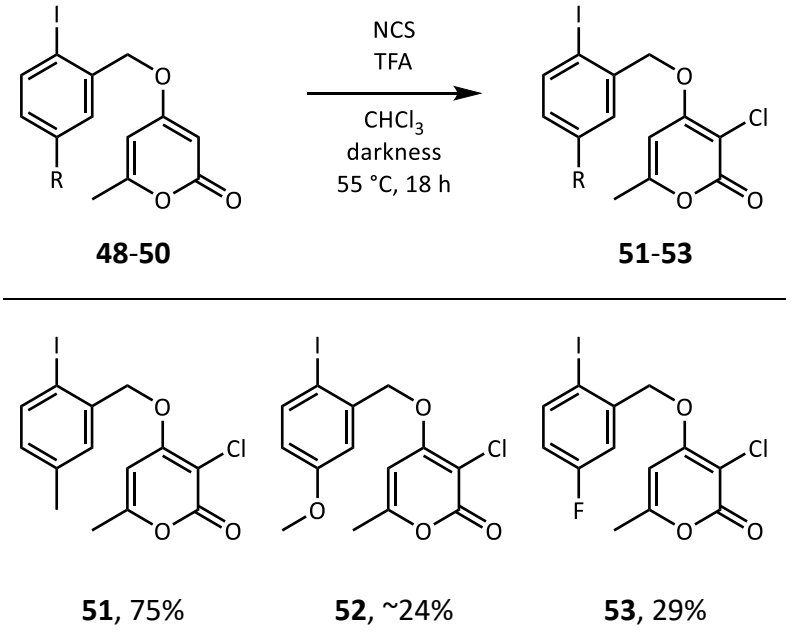
Successful product formation was determined by NMR spectroscopy, with the disappearance of the C–3 proton at 5.50 ppm, and the downfield shift of the C–5 proton in the ^{1}H NMR spectrum due to the deshielding effect of the inductively electron-withdrawing chloride. In the ^{13}C NMR spectrum, the disappearance of a CH peak at 88.8 ppm and the appearance of a quaternary carbon peak at 100.5 ppm confirmed that chlorination had occurred. The C–5(H) peak shifted upfield from 100.3 ppm to 96.1 ppm. Selective chlorination at the C–3 position was achieved, and no C–5 chlorinated product was observed.

To investigate the scope of the reaction, further substrates related to **4** were prepared in a similar fashion, using substituted 2-iodobenzylbromides (**Scheme 2.22**). The desired mono-benzylated products were purified from the crude reaction mixture by column chromatography on silica gel. This was relatively trouble-free in the case of **48** and **50**, however only a 4% isolated yield of **49** was achieved due to problems with co-elution of a dibenzylated side-product similar to that described in **Section 2.2.1**.



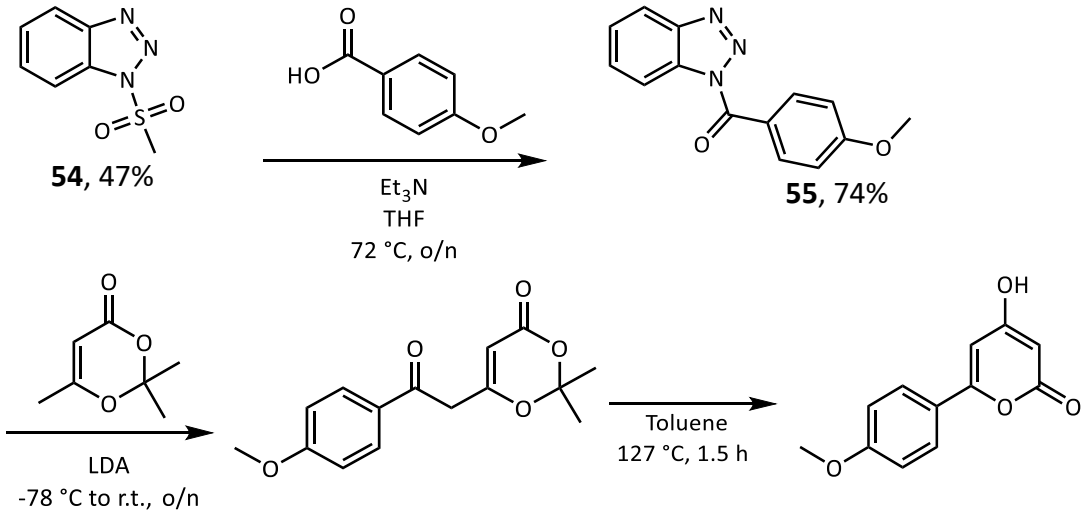
Scheme 2.22. Synthesis of substituted aryl substrates **48**-**50**.

The pure benzylated 2-pyrones **48** and **50** were then chlorinated using NCS in the presence of TFA (**Scheme 2.23**) to give the desired substrates **51** and **53**. The crude reaction mixture containing **49** was also subjected to these chlorination conditions. In the latter case, the difference in polarity between the chlorinated product **52** and the dibenzylated side-product was sufficient to allow the isolation of **52** in approx. 24% yield (based on impure starting material).



Scheme 2.23. Chlorination of substrates **48**-**50**.

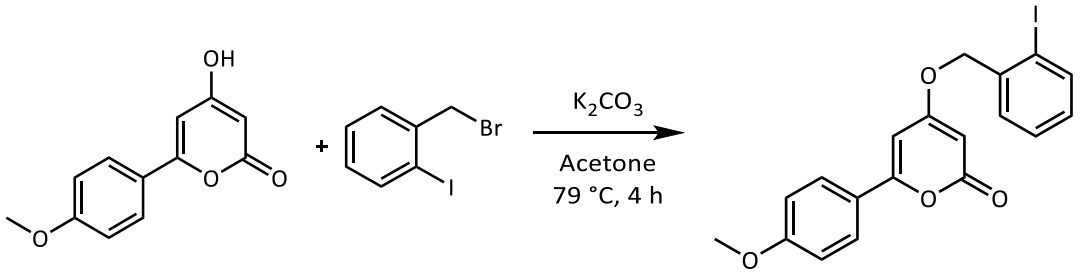
4-Hydroxy-6-(4-methoxy)phenyl-2-pyrone (**57**) was prepared by a method developed by Katritzky *et al.*,[44] as shown in **Scheme 2.24**.



Scheme 2.24. Synthesis of 4-hydroxy-6-(4-methoxy)phenyl-2-pyrone (**57**).

The *N*-acylbenzotriazole **55** was prepared in 74% yield by treating *p*-methoxyphenylcarboxylic acid with 1-(methylsulfonyl)-1*H*-1,2,3-benzotriazole (**54**) in the presence of Et_3N under reflux overnight. Treatment of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one with LDA and subsequent reaction with *N*-acylbenzotriazole **55**, initially at −78 °C and warming to ambient temperature overnight, yielded **56** in a very poor 6% yield. Finally, a solution of **56** was heated in toluene for 1.5 h at 127 °C, resulting in the formation of the 4-hydroxy-2-pyrone **57** in 59% isolated yield after column chromatography on silica gel.

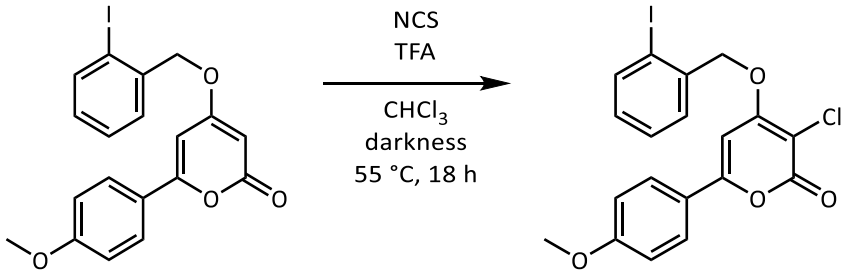
4-Hydroxy-6-(4-methoxy)phenyl-2-pyrone (**57**) was benzylated with dihalide **2** and the mono- and di-benzylation products were easily separated by column chromatography on silica gel to give **58** in 42% yield (**Scheme 2.25**).



57 **2** **58**, 42%

Scheme 2.25. Benzylation of 4-hydroxy-6-(4-methoxy)phenyl-2-pyrone (**57**).

The benzylated 2-pyrone **58** was chlorinated with NCS in the presence of TFA to give the target substrate in 49% yield after chromatography on silica gel (**Scheme 2.26**).



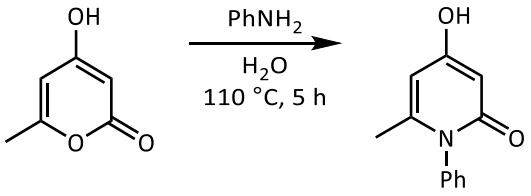
58 **59**, 49%

Scheme 2.26. Chlorination of 2-pyrone **58**.

2-Pyridones

We were interested to see if the direct arylation conditions would also be suitable for the C–5 arylation of 2-pyridones, which has not been previously reported, and which was unsuccessful using the previous direct arylation/hydrodebromination conditions which had been successful with 2-pyrone substrate **46**.[7] To this end, some 2-pyridone substrates were prepared.

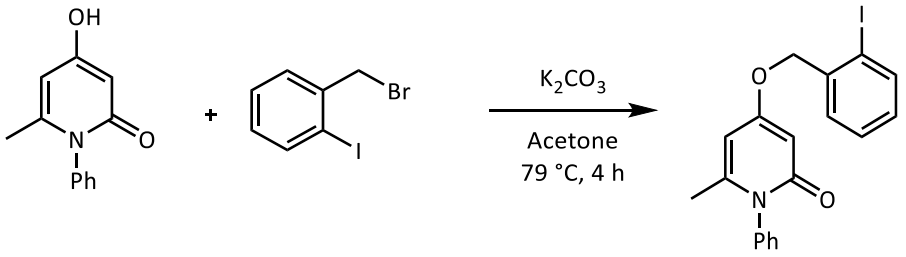
The synthesis of *N*-methyl-4-hydroxy-2-pyridone substrate **16** was previously described in **Section 2.2.1.** The *N*-phenyl-4-hydroxy-2-pyridone substrate was prepared in a similar fashion. Thus, *N*-phenyl-4-hydroxy-2-pyridone **60** was synthesised from 4-hydroxy-6-methyl-2-pyrone **3**, using aniline as the amine source, in 23% yield (**Scheme 2.27**).



3 **60**, 23%

Scheme 2.27. Synthesis of *N*-phenyl-4-hydroxy-2-pyridone **60**.

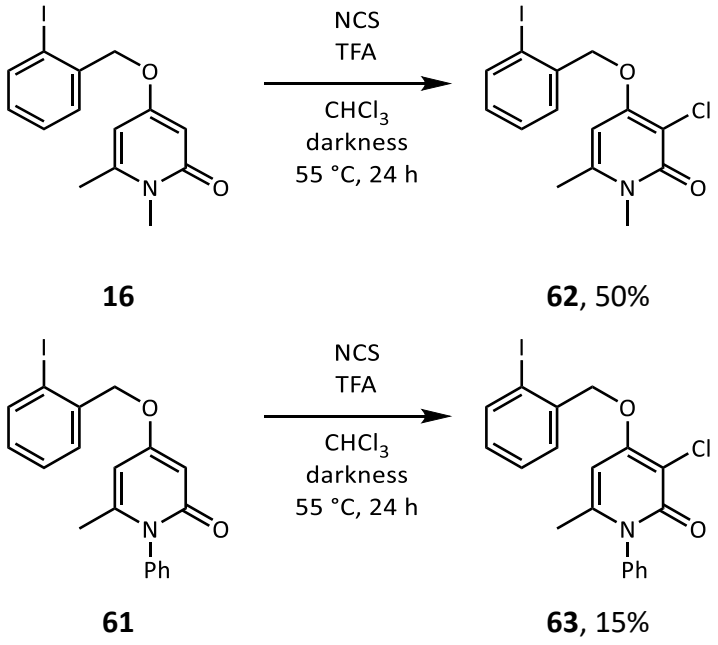
Once synthesised, **60** was benzylated using the reported procedure,[13] giving **61** in 78% yield after column chromatography on silica gel (**Scheme 2.28**).



60 **2** **61**, 78%

Scheme 2.28. Benzylation of *N*-phenyl-4-hydroxy-2-pyridone **60**.

The benzylated 2-pyridones **16** and **61** were chlorinated with NCS in the presence of TFA to give the target compounds in 50% and 15% yields respectively after purification (**Scheme 2.29**).



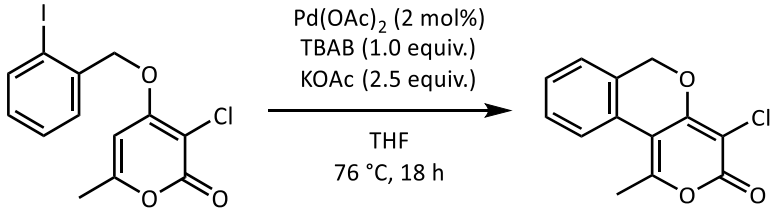
16 **62**, 50%

61 **63**, 15%

Scheme 2.29. Chlorination of *N*-substituted 2-pyridones.

2.3.2. Optimisation of reaction conditions for C–5 arylation

Initial investigation of the direct arylation of substrate **47** was performed by another member of the McGlacken group,[45] and it was determined that the catalytic system shown in **Scheme 2.30** allowed C–5 arylation with retention of the 3–Cl bond to give **64** in very good yield.

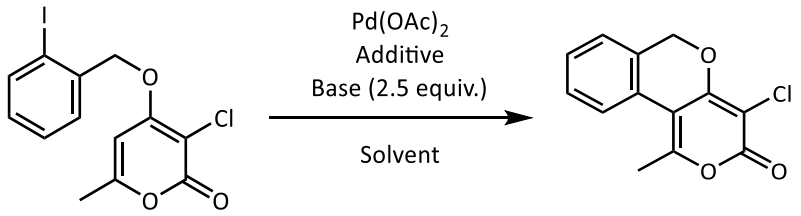


47 **64**, 85%

Scheme 2.30. Direct arylation conditions discovered by the McGlacken group.[45]

Further investigation of these conditions (**Table 2.2**) showed that no improvement over the conditions shown in **Scheme 2.30** could be achieved. Attempts to scale up the synthesis of **64** to >100 mg with 2 mol% $Pd(OAc)_2$ gave disappointing results. Large amounts of residual starting material and so-called "Pd black" was observed in the reaction mixture. Tetraalkylammonium halides such as TBAB have been shown to stabilise colloidal Pd clusters.[46] Such colloidal clusters serve as a reservoir for catalytically active Pd nanoparticle (NP) species.[47] It is possible that the presented reaction is mediated by Pd NPs. It has been reported that low, "homeopathic" Pd concentrations were required to prevent agglomeration of colloidal clusters, and thus inhibit the formation of insoluble Pd(0) black.[48] However, in our case, reducing the Pd loading from 2 mol% to 0.5 mol% (**Table 2.2**, **entry 2**) inhibited conversion. Thus, the presented catalytic system is a delicate balance between the minimum quantity of Pd required to efficiently catalyse the reaction, and the maximum quantity of Pd which can be employed before aggregation.

Table 2.2. Investigation of C–5 direct arylation conditions.

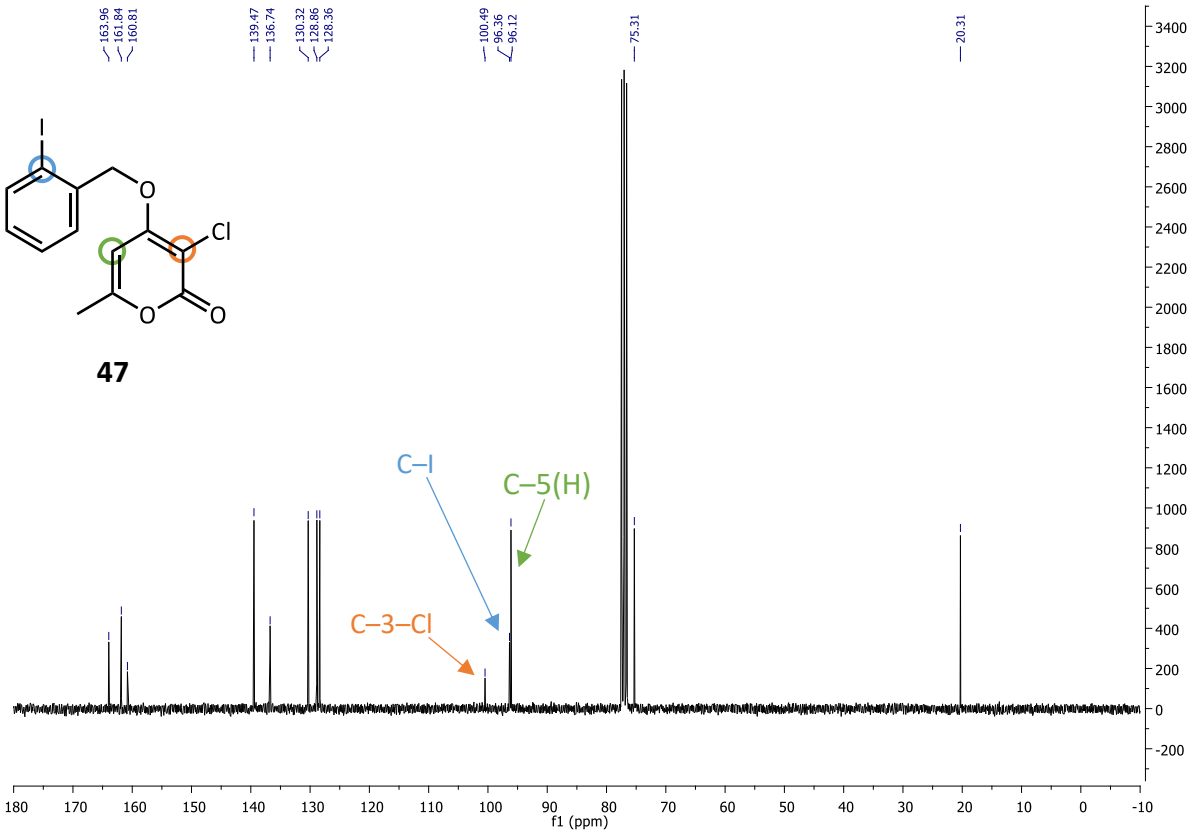


47 **64**

Entry	$Pd(OAc)_2$ mol%	Additive (equiv.)	Base	Solvent	T (°C)	Time (h)	Yield or Conversion (%)
1	2	TBAB (1.0)	KOAc	THF	76	18	85[a]
2	0.5	TBAB (1.0)	KOAc	THF	76	16	16[b]
3	5	SPhos (0.15)	KOAc	Toluene	127	23	9[b]
4	2	TBAB (1.2)	KOAc	1,4-Dioxane	100	21	43[c]

[a]Isolated yield. [b]Conversion calculated from ratio of starting material **47** to product **64** in ^{1}H NMR spectrum of the crude reaction mixture. [c]Yield determined from the ^{1}H NMR spectrum of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard for quantification.

The direct arylation at C–5 to give **64** was confirmed using NMR spectroscopy. In the ^{1}H NMR spectrum of **64**, the C–5 proton at 6.06 ppm observed in **47** was not present. In the ^{13}C spectrum, the CH peak at 96.1 ppm had disappeared, and a new quaternary carbon peak was observed at 107.8 ppm (**Figure 2.2**).



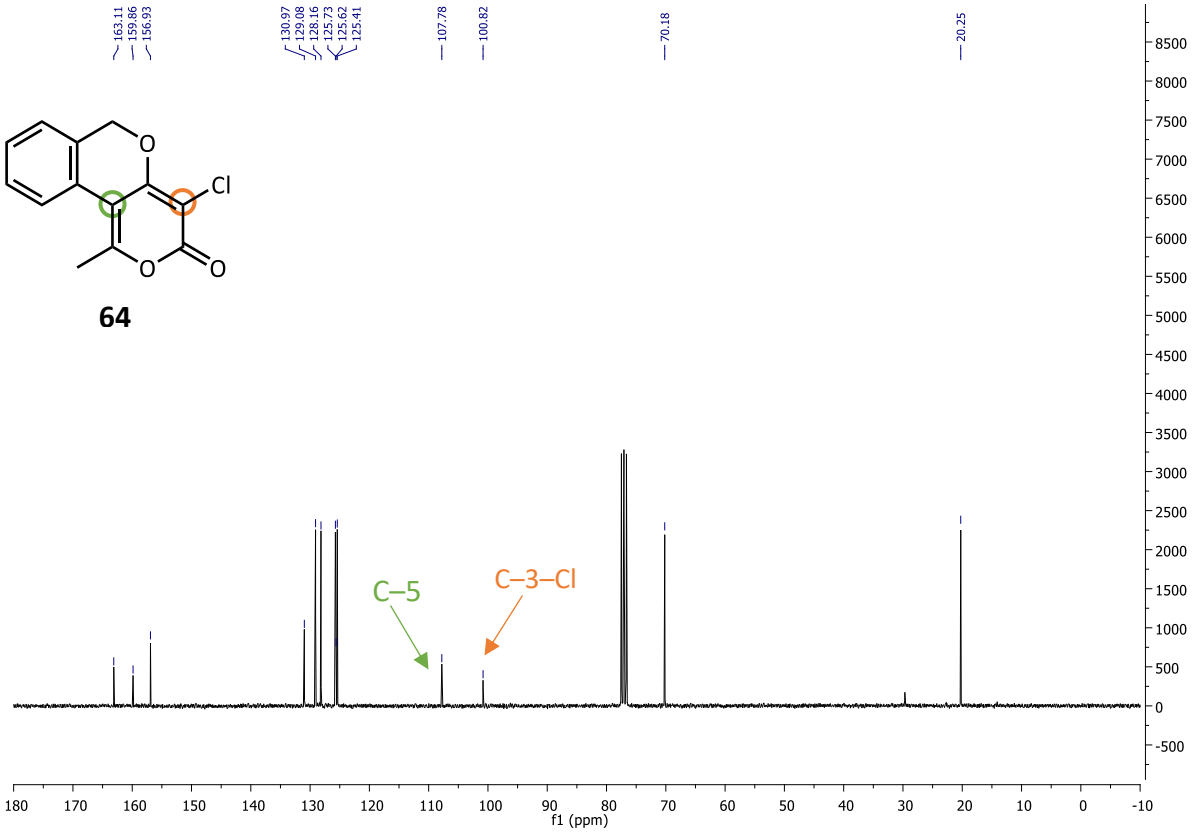
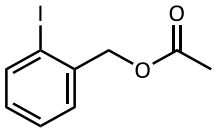


Figure 2.2. Comparison of ^{13}C NMR spectra of **47** and **64**.

An impurity peak was observed at 5.13 ppm in the ^{1}H NMR spectra of the crude reaction mixtures in all reactions shown in **Table 2.2**. However, the amount of this impurity greatly increased when the reaction was performed in 1,4-dioxane (**Table 2.2**, **entry 4**). The impurity was isolated after column chromatography on silica gel. With the aid of ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry data in consultation with the literature,[49] the impurity was determined to be 2-iodobenzyl acetate **65**.



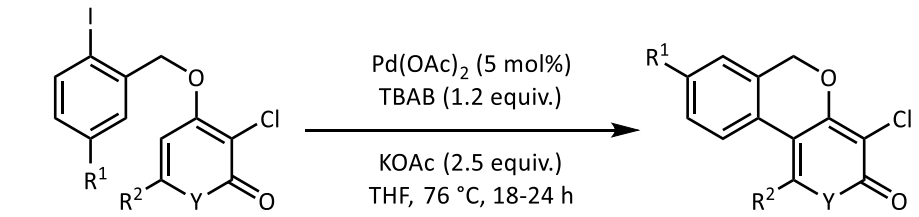
65

Figure 2.3. Impurity isolated from reaction mixture.

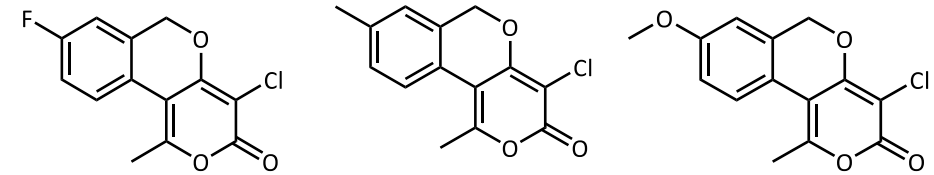
This impurity is most likely formed from attack of the acetate anion at the benzylic carbon of **47**. The acetate would be stabilised by the more polar 1,4-dioxane which explains the increased levels of this impurity in this solvent (65:35, **64**:**65**) compared to THF (91:9, **64**:**65**). The formation of **65** or related impurities could be prevented by use of a less nucleophilic base. However, since the levels of impurity formation were low in the optimised conditions (**Table 2.2**, **entry 1**) and the yield was excellent at 85%, it was determined to proceed with KOAc as the base. Our optimised conditions were therefore 2 mol% $Pd(OAc)_2$, 1.0 equiv. TBAB, 2.5 equiv. KOAc in THF at 76 °C for 18 h. We next sought to test the tolerance of the methodology to changes in substrate, and a short scope was investigated.

2.3.3. Demonstration of substrate scope for C–5 arylation

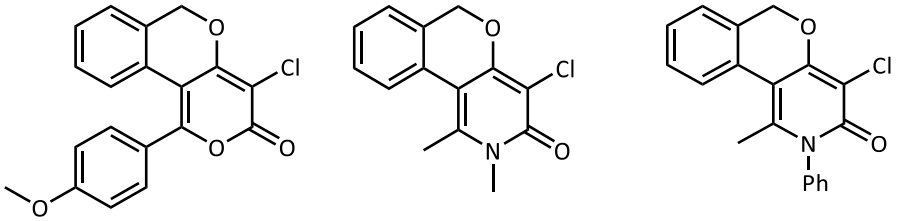
The synthesis of the target substrates is described in **Section 2.3.1**. Due to the small scale (approx. 0.1 mmol), the physical amount of $Pd(OAc)_2$ required for a 2 mol% loading was too small (<0.5 mg) to be consistently measured out. Thus, to ensure reproducibility, the catalytic loading was increased to 5 mol% $Pd(OAc)_2$ for the scope investigation, and 1.2 equiv. TBAB was used.



51-**53**, **59**, **62**-**63** **69**-**71**



66, 43% **67**, 53% **68**, 63%



69, 0% **70**, 55% **71**, 60%

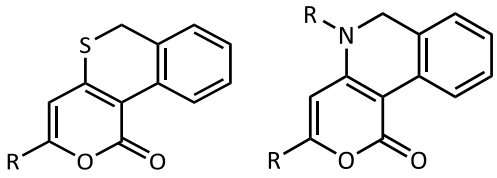
Scheme 2.31. Substrate scope for C–5 arylation conditions.

Pleasingly, a number of substrates were well tolerated under the reaction conditions (**Scheme 2.31**). Substituents *para* to the oxidative addition site worked well, with a *p*-fluoro substituent giving product **66** in 43% yield, a *p*-methyl substituent giving product **67** in 53% yield, and a *p*-methoxy substituent giving product **68** in 63% yield.

Importantly, and in contrast to previous studies,[7] the 2-pyridone substrates **62** and **63** also coupled well, giving the desired products **70** and **71** in moderate yields. However, employing a bulky substituent in the 6-position (**59**) failed to give any product **69**, presumably due to unfavourable steric interactions at palladium during the catalytic cycle, or at carbon in the product.

2.4. Investigation of novel linkers for direct arylation at C–3

With the success in constructing new ring systems on the 2-pyrone framework, we were interested in testing if our methodology could be expanded to include different heteroatom linkers, for example, to form benzothiophenylpyrones **72** or benzoaminophenylpyrones **73** (**Figure 2.4**).

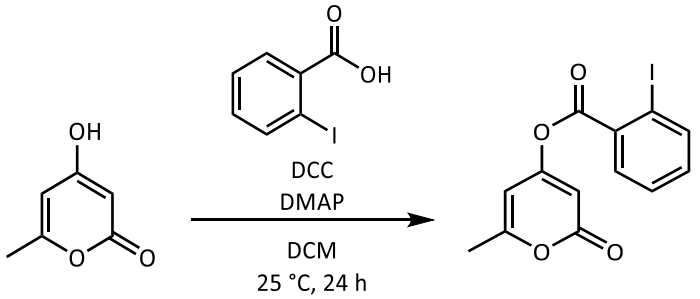


72 **73**

Figure 2.4. Benzothiophenylpyrones and benzoaminophenylpyrones.

A previous publication from the Fairlamb group on the formation of five-membered rings has shown that when the character of the intramolecular linker is changed, it can completely shut down the catalytic system.[50] We decided to prepare a variety of intramolecular linkers to test if the same effect would be observed in our systems for the formation of new six-membered rings.

Thus, a 2-pyrone possessing an ester linkage was synthesised in 81% yield from 2-pyrone **3** *via* a Steglich esterification (**Scheme 2.32**).[51] The Steglich esterification involves a *N,N'*-dicyclohexylcarbodiimide (DCC)-activated esterification of carboxylic acids with alcohols or thiols. A catalytic quantity of 4-dimethylaminopyridine (DMAP) suppresses the formation of *N*-acylurea side-products.

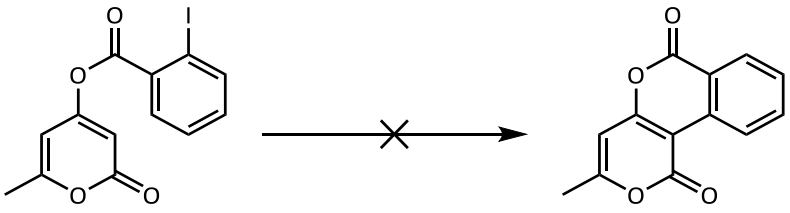


3 **74**, 81%

Scheme 2.32. Steglich esterification to **74**.

This substrate was subjected to four different direct arylation conditions which have been developed in the McGlacken group (**Table 2.3**). In all cases, only ester hydrolysis of the starting material was detected to give **3** and 2-iodobenzoic acid.

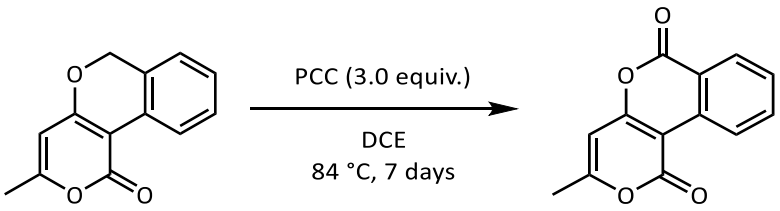
Table 2.3. Attempted direct arylation of **74**.



74 **75**

Entry	Conditions	Result
1[26]	$Pd_2(dba)_3$, PPh_3, PivOH, Na_2CO_3, NMP, 129 °C, 3 h	Degradation of **74**
2	$Pd_2(dba)_3$, PPh_3, Na_2CO_3, NMP, 129 °C, 2 h	Degradation of **74**
3	$Pd(OAc)_2$, PPh_3, Na_2CO_3, NMP, 129 °C, 2 h	Degradation of **74**
4[7]	$Pd(OAc)_2$, TBAB, KOAc, Toluene, 127 °C, 2 h	Complex Mixture

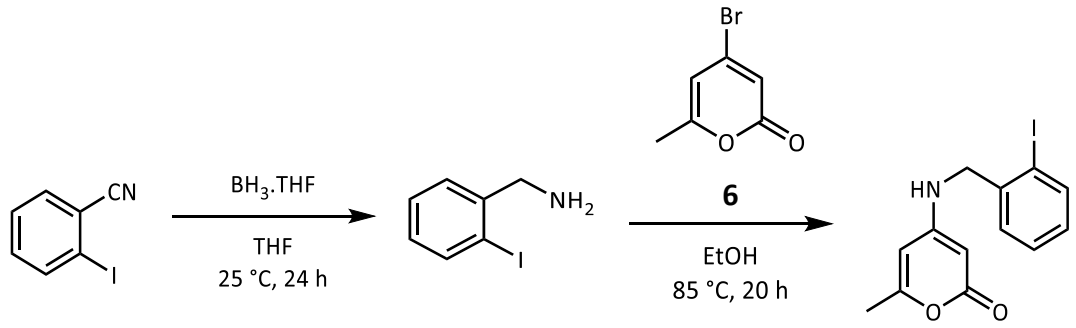
Although the direct arylation was unsuccessful, we were able to access **75**, albeit in a poor yield of 26%, by oxidation of **31** using pyridinium chlorochromate (PCC) (**Scheme 2.33**).



31 **75,** 26%

Scheme 2.33. Oxidation of 2-pyrone **31** with PCC.

Next, we sought to test an amino linker because nitrogen-containing heterocycles are ubiquitous in biologically active compounds, and the ability to form *N*-containing heterocycles by direct arylation would be a highly useful transformation. The synthesis of the substrate involved reduction of the cyano group of **76** to a primary amine **77** using BH_3.THF in 29% yield. The amine **77** was subsequently reacted with 4-bromo-2-pyrone to give the desired substrate **78** in 85% yield (**Scheme 2.34**).

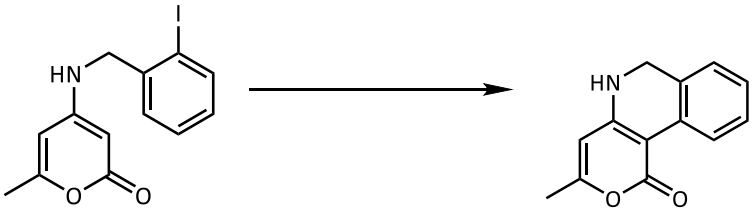


76 **77**, 29% **78**, 85%

Scheme 2.34. Synthesis of substrate **78**.

A variety of direct arylation conditions that had been developed in the group were again applied to **78**, however, none gave very encouraging results (**Table 2.4**). Only a trace of **79** could be detected in the ^{1}H NMR spectrum of the crude reaction mixture (**Table 2.4**, **entry 3**). However, it was not possible to isolate the compound from the reaction mixture. The poor reactivity of **78** may be due, at least in part, to ligand effects of the free N–H to Pd. This likely shuts down the catalytic cycle by competing with the C–I bond for Pd. Due to the poor results, this line of investigation was not pursued further.

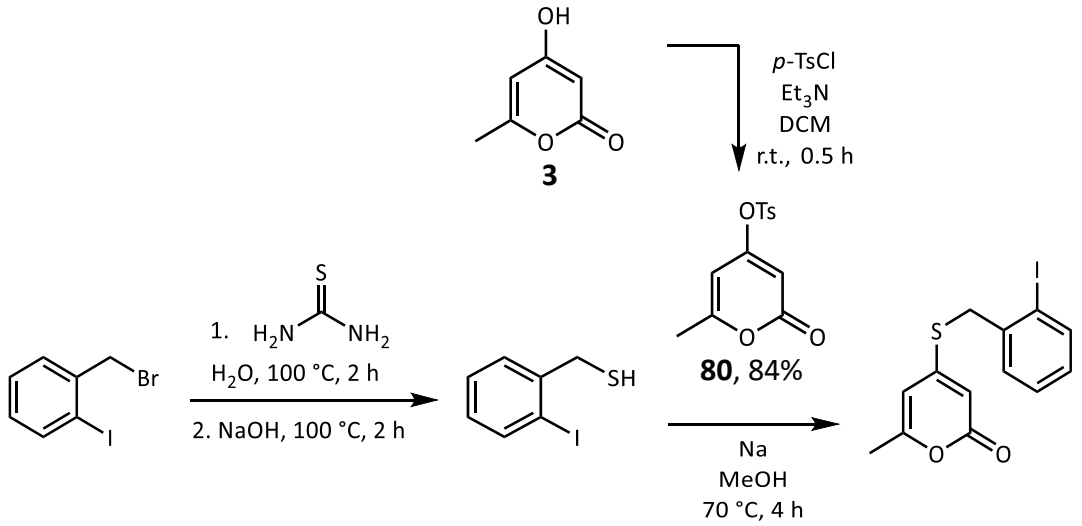
Table 2.4. Attempted direct arylation of **78**.



78 **79**

Entry	Conditions	Result
1[26]	$Pd_2(dba)_3$, PPh_3, PivOH, Na_2CO_3, NMP, 129 °C, 24 h	Degradation of **78**
2	$Pd_2(dba)_3$, PPh_3, Na_2CO_3, NMP, 129 °C, 24 h	Unreacted **78**
3[7]	$Pd(OAc)_2$, TBAB, KOAc, Toluene, 127 °C, 24 h	Trace of **79** and unreacted **78**

Finally, we sought to test a thio-linker, which was synthesised according to **Scheme 2.35**. A 4-tosyloxy 2-pyrone **80** was synthesised from 4-hydroxy 2-pyrone **3** and *p*-tosylchloride in 84% yield. Dihalide **2** was reacted with thiourea to give an intermediate isothiourea which was hydrolysed with aqueous NaOH to give 2-iodobenzylthiol (**81**) in 64% yield. Reaction of **81** with 4-tosyloxy 2-pyrone **80** gave substrate **82** in 50% yield.

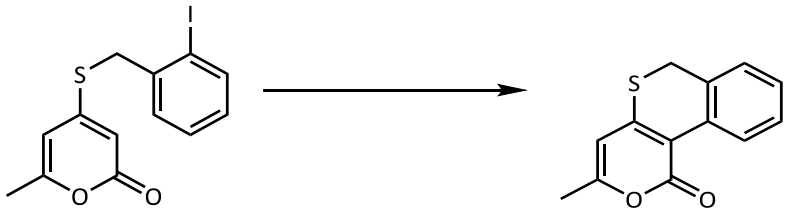


Scheme 2.35. Synthesis of thio-linker **82**.

Substrate **82** was subjected to a number of direct arylation conditions previously developed in the McGlacken group (**Table 2.5**). In some cases (**Table 2.5**, **entry 1** and **Table 2.5**, **entry 2**), only degradation of the substrate **82** was observed. However,

using so-called Jeffery's conditions (**Table 2.5**, **entry 3**), it was possible to isolate **83** in 21% yield. In the latter case, unreacted starting material **82** was also observed in the ^{1}H NMR spectrum of the crude reaction mixture.

Table 2.5. Direct arylation of **82**.



82 **83**

Entry	Conditions	Result
1[26]	$Pd_2(dba)_3$, PPh_3, PivOH, Na_2CO_3, NMP, 129 °C, 4 h	Degradation of **82**
2	$Pd_2(dba)_3$, PPh_3, Na_2CO_3, NMP, 129 °C, 24 h	Degradation of **82**
3[7]	$Pd(OAc)_2$, TBAB, KOAc, Toluene, 127 °C, 16 h	21% isolated yield of **83** and unreacted **82**

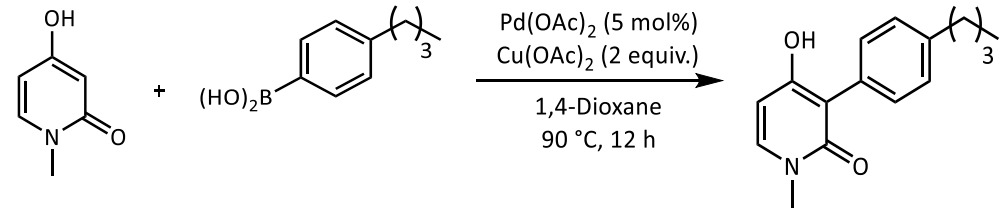
Again, the ligand effect of the sulfur towards Pd is likely to be the reason for the poor success of this reaction. The action of sulfur as a Pd catalyst poison is well documented in the literature.[52-53]

In summary, changes to the linker shut down the catalytic systems for direct arylation which have been developed by the McGlacken group. In the case of the ester linker, only ester hydrolysis of the starting material was observed. While traces of the desired products were observed in the reactions of the amino- and thio-linkers, the results were not deemed to be positive enough to continue with this line of investigation.

2.5. Intermolecular direct arylation

Having successfully developed a number of protocols to effect the intramolecular direct arylation of 2-pyrones and related heterocycles, we turned our attention towards intermolecular direct arylation. For this section, we focused on the intermolecular direct arylation of 2-coumarins, since they are more robust than the corresponding 2-pyrones.

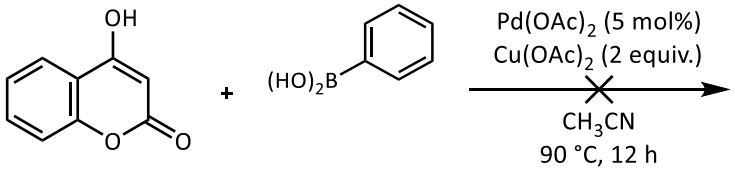
The intermolecular C–3 direct arylation of 4-hydroxy-2-pyridones has been described by Zografos (**Scheme 2.36**).[54]



84 (3 equiv.) **85**, 89%

Scheme 2.36. Zografos' intermolecular direct arylation of 4-hydroxy-2-pyridone **84**.

We were curious as to whether similar conditions would faciliate the intermolecular direct arylation of 4-hydroxy-2-coumarin (**19**). Applying the conditions reported by Zografos[54] resulted in degradation of the 2-coumarin starting material while the $PhB(OH)_2$ remained unreacted (**Scheme 2.37**).

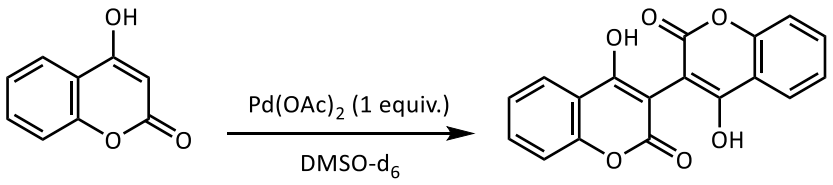


19 (3 equiv.)

Scheme 2.37. Application of Zografos' conditions to 4-hydroxy-2-coumarin **19**.

Rather than varying the reaction conditions, it was decided to initially investigate if 2-coumarin **19** was a competent starting material for this transformation, *i.e.* if it could participate in oxidative addition by Pd. Zografos had reported that a palladated intermediate derived from 2-pyridone **84** was observed by ^{1}H NMR analysis.[54] Therefore, the ability of **19** to undergo oxidative addition by $Pd(OAc)_2$ was tested by mixing a stoichiometric amount of palladium and **19** in DMSO-d_6 in an NMR tube (**Scheme 2.38**). A reduction in the integral of the C–3 proton at 5.60 ppm relative to the aromatic protons would have been considered evidence that oxidative addition had occurred. The ^{1}H NMR spectrum of the 2-coumarin/$Pd(OAc)_2$ mixture showed peaks corresponding to both **19** and dicoumarin **86**. Evidence for the presence of

dicoumarin **86** was also observed in the nominal mass spectrum of the reaction mixture after it had been filtered through Celite®.

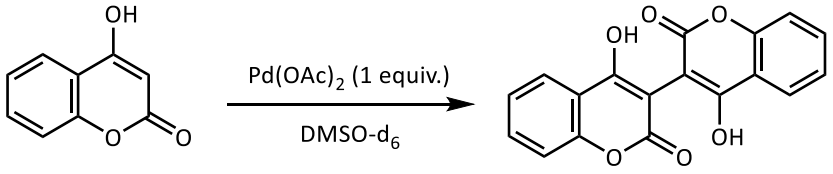


19 **86**

Scheme 2.38. Oxidative addition of palladium into C–3–H bond of **19**.

Zografos observed that dipyridone formation was pH-dependent.[54-55] Therefore, the procedure illustrated in **Scheme 2.38** was repeated and compared under acidic and basic conditions (**Table 2.6**). In the presence of K_2CO_3, only dicoumarin **86** was observed with no trace of starting material **19**. The use of formic acid completely suppressed dicoumarin formation. However, it also appeared to suppress oxidative addition.

Table 2.6. Effect of acidic and basic conditions on dicoumarin **86** formation.

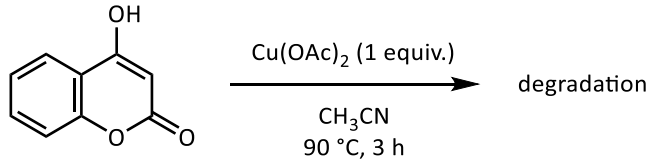


19 **86**

Additive	Conversion to dicoumarin 86
–	Trace (*ca.* 5%)
HCOOH	0%
K_2CO_3	100%

In any case, a variety of reaction conditions related to those shown in **Scheme 2.38** were tested, but none gave any evidence of C–3 arylation. However, it was observed that using a catalytic rather than stoichiometric quantity of copper oxidant, gave reactions with fewer degradation products. This led us to suspect that perhaps copper was degrading the 2-coumarin framework. To confirm that copper was the reason for the degradation, the experiment shown in **Scheme 2.39** was performed.

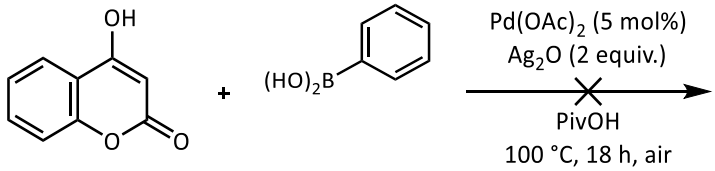
The starting material was heavily degraded and it was concluded that copper salts were not suitable oxidants for this 2-coumarin substrate.



19

Scheme 2.39. Effect of copper salts on 2-coumarin **19**.

Finally, a similar reaction using Ag_2O as the oxidant was tried (**Scheme 2.40**). Unfortunately, only the starting 2-coumarin and boronic acid were observed in the ^1H NMR spectrum of the crude reaction mixture, but no degradation of the 2-coumarin was observed.



19 (3 equiv.)

Scheme 2.40. Attempted intermolecular direct arylation of **19** with silver oxidant.

Further development of this reaction is required, potentially involving an oxidant screen under neutral conditions.

2.6. Conclusions and Future Work

The regioselective intramolecular cyclisation of the privileged 2-pyrone, 2-pyridone and 2-coumarin motifs under direct arylation conditions has been developed. For intramolecular cyclisation at C–3, a broad substrate scope and good to excellent yields were achieved. Further insight into the mechanism of this reaction will be discussed in **Chapter 4**. For the intramolecular cyclisation at C–5, a methodology which allows the preparation of some previously inaccessible 2-pyrones and 2-pyridones was developed. The reactions proceed *via* direct arylation with retention of a C–Cl bond. Substituents *para* to the site of oxidative addition were well tolerated

by the reaction conditions. The further cross-coupling of the retained C–Cl bond will be discussed in **Chapter 3**. Attempts to vary the linker were relatively unsuccessful. The reported conditions for the intermolecular direct arylation of 4-hydroxy-2-pyridones do not facilitate the same transformation in 4-hydroxy-2-coumarins. Homocoupling of the 2-coumarin **19** to give dicoumarin **86** occurs under basic conditions, and copper salts cause degradation of the 2-coumarin motif.

Future work in this area will likely examine the application of direct arylation conditions, particularly intermolecular direct arylation and cross-dehydrogenative coupling, to the synthesis of natural products and other biologically active compounds. To date, C–H activation is rarely employed in total synthesis or fine chemical manufacture, particularly as an end-game strategy. This may be due to the harsh conditions typically required. It is hoped that by describing C–H activation as it has been applied to several classes of biologically interesting but chemically sensitive motifs: the 2-pyrones, 2-pyridones and 2-coumarins, efforts will be focused towards milder conditions for C–H activation and cross-dehydrogenative coupling. In general, it is anticipated that future development of C–H activation methodology will focus on using Earth-abundant metal catalysts such as iron, manganese and cobalt, rather than precious metal catalysts including palladium and rhodium.

2.7. References

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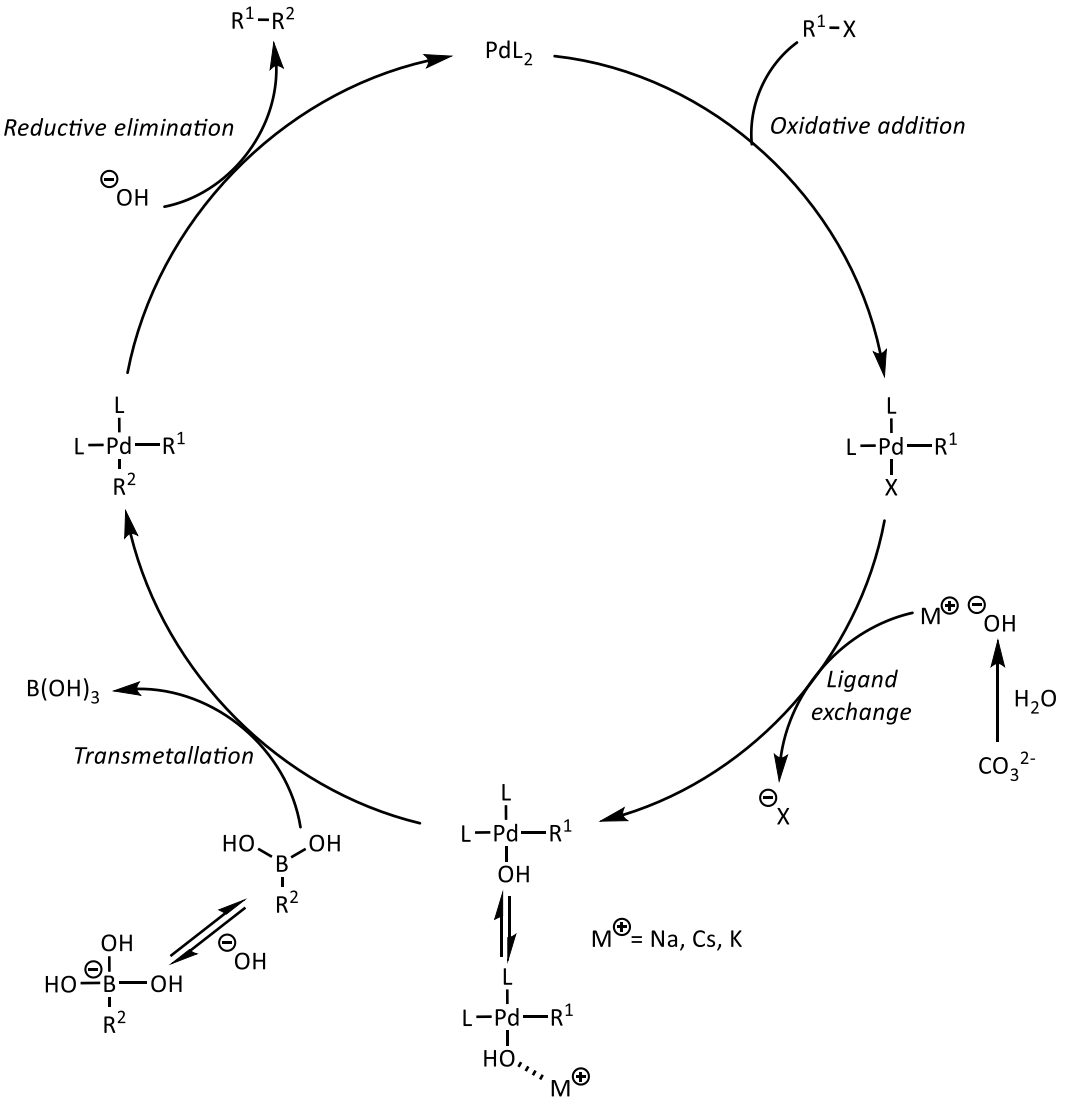
Chapter 3: Suzuki-Miyaura cross-coupling of 2-pyrones and related heterocycles

Dripping water hollows out stone, not through force but through persistence.

Ovid

3.1. Introduction

The formation of aryl-heteroaryl (Ar-HetAr) bonds is an important transformation in organic synthesis[1] due to the abundance of the Ar-HetAr moiety in natural products and pharmaceuticals.[2] One of the most widely employed methods for the formation of Ar-HetAr bonds is the Suzuki-Miyaura reaction,[3-5] which involves the cross-coupling of an organohalide and an organoboron species[6] in the presence of palladium, usually utilising phosphine ligands, and a suitable base. The reaction was first published by Akira Suzuki in 1979,[7] and he shared the 2010 Nobel Prize in Chemistry with Richard F. Heck and Ei-ichi Negishi.[8] The mechanism of the Suzuki-Miyaura has been proposed as follows (**Scheme 3.1**): oxidative addition of the organohalide to the catalytically active Pd(0) species initiates the catalytic cycle. A hydroxide or alkoxide base then replaces the halide on the Pd complex. Transmetallation of the organoboron species with the Pd complex gives a Pd(II) intermediate bearing the two organic coupling partners. Subsequent reductive elimination results in C–C bond formation with the Pd(0) species available to re-enter the catalytic cycle.



Scheme 3.1. General mechanism of the Suzuki-Miyaura cross-coupling reaction.

The base has recently been discovered to fulfil several key, yet antagonistic, roles in the Suzuki-Miyaura reaction.[9] Two are positive and facilitate the progression of the reaction: Formation of *trans*-[$PdR^1L_2(OH)$] that reacts with $R^2B(OH)_2$ in the (usually) rate-determining transmetallation step, and facilitation of the reductive elimination of Pd(0) from *trans*-[$PdR^1R^2L_2$]. Two pathways can inhibit the reaction: Formation of unreactive anionic borates, and complexation of the OH group of [$PdR^1L_2(OH)$], in this case by the counterion of the base (*e.g.* Na^+, K^+, Cs^+). It was also found that optimisation of the base is less crucial when oxidative addition is the rate-determining step, *e.g.* when aryl chlorides are used as the organohalide coupling partner.[9] Iodide and bromide are largely preferred as the organohalide partner due

to their reactivity, however, organochlorides are more attractive substrates from a cost and availability viewpoint.[10]

The advantages offered by the Suzuki-Miyaura reaction over other methods of C–C bond formation include mild reaction conditions, good accessibility and stability of organoboron reagents, a high tolerance towards a variety of functional groups (especially sterically demanding substrates) and a low toxicity profile of both the starting materials and side products.[11] An engaging review of the field of cross-coupling chemistry in 2012[12] highlights the developments from the original discoveries to the prominent position of the Suzuki-Miyaura reaction in modern synthetic chemistry.

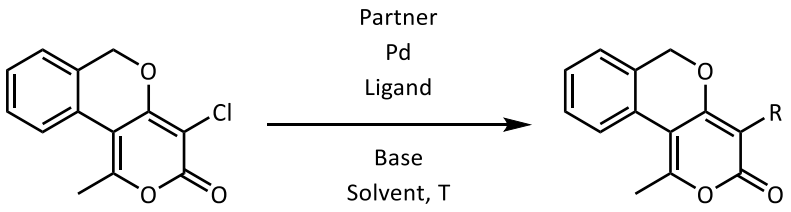
3.2. Cross-coupling of direct arylation product 64

In **Section 2.3**, the development of a direct arylation methodology which facilitated retention of a C–Cl bond to give the cyclised 3-chloro 2-pyrone **64** was described. In this section, the development of conditions to facilitate the further cross-coupling at this position will be discussed.

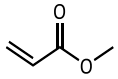
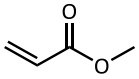
3.2.1. Optimisation of cross-coupling conditions

The objective of this work was to demonstrate that although the C–Cl bond at C–3 was stable enough to withstand the conditions of the direct arylation reaction, it remained reactive enough to participate in further reactions. Initially, a variety of cross-coupling conditions which had been reported for the functionalisation of aryl chlorides were tested (**Table 3.1**).

Table 3.1. Exploration of cross-coupling conditions.



64

	Partner (equiv.)	Pd (mol%)	Ligand (mol%)	Base (equiv.)	Solvent	T (°C)	t (h)	Result
1	 (1.2)	$Pd(OAc)_2$ (5)	$PCy_3.HBF_4$ (15)	K_2CO_3 (3.0)	Xylenes	130	15 36 134	unreacted **64** degradation degradation
2	 (1.0)	$Pd_2(dba)_3$ (1.5)	$PtBu_3.HBF_4$ (6)	K_2CO_3 (1.1)	1,4-dioxane	120	15 36 134	unreacted **64** degradation degradation
3	nBu_3SnPh (1.05)	$Pd_2(dba)_3$ (1.5)	$PtBu_3.HBF_4$ (6)	CsF (2.2)	1,4-dioxane	120	15 36 134	unreacted **64** unreacted **64** **64** (26%[a])

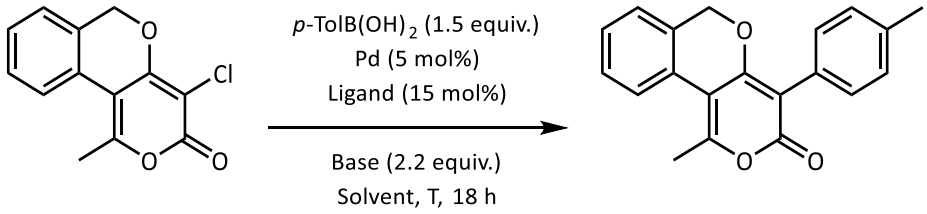
[a]Yield determined from the ^{1}H NMR spectrum of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard for quantification.

Heck-type conditions (**Table 3.1**, **entry 1**[13] and **Table 3.1**, **entry 2**[14]) gave degradation of the starting material and no product was detected by ^{1}H NMR spectroscopy. Stille conditions (**Table 3.1**, **entry 3**)[15-16] also gave degradation of the starting material. A 26% recovery of the unreacted starting material **64** was measured from the ^{1}H NMR spectrum of the crude reaction mixture after 5 days under the Stille conditions, (using 1,3,5-trimethoxybenzene as the internal standard for quantification) and no product was observed.

Therefore, it was decided to focus on the Suzuki-Miyaura cross-coupling reaction. Despite the development of modern methods such as direct arylation,[17] the Suzuki-Miyaura reaction remains the most common palladium-catalysed transformation for large-scale synthesis of drug candidates.[18] It was expected that the plethora of conditions reported for the Suzuki-Miyaura cross-coupling of aryl

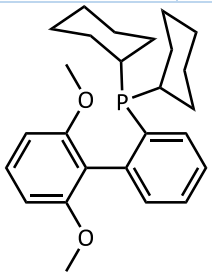
chlorides could be harnessed, and it was with these conditions that the optimisation study (**Table 3.2**) began.

Table 3.2. Optimisation of Suzuki-Miyaura cross-coupling conditions.

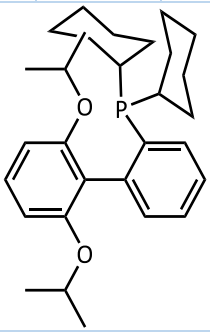


64 **87**

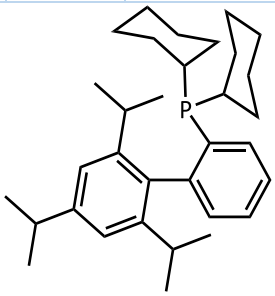
	Pd	Ligand	Base	Solvent	T (°C)	Conv. (%)[a]
1[b]	$Pd_2(dba)_3$	P(*t*Bu)$_3$.HBF$_4$	KF	THF	60	0
2[c]	$Pd(OAc)_2$	DavePhos	CsF	Dioxane	110	0
3	$Pd(OAc)_2$	SPhos[d]	K_2CO_3	Toluene	110	60
4	$Pd(OAc)_2$	SPhos[d]	KOAc	Toluene	110	70
5	$Pd(OAc)_2$	SPhos	KOAc	2-MeTHF	90	69
6	$Pd(OAc)_2$	SPhos	KOAc	Dioxane	110	44
7	$Pd_2(dba)_3$	SPhos	KOAc	THF	76	6
8	$Pd(OAc)_2$	RuPhos	KOAc	THF	76	64
9	$Pd(OAc)_2$	XPhos	KOAc	THF	76	29
10	$Pd(OAc)_2$	SPhos	KOAc	THF	76	93 (92)



SPhos



RuPhos



XPhos

[a]Conversion from starting material to product was calculated from ^{1}H NMR spectra of crude reaction mixture. Isolated yields in parenthesis. [b]$Pd_2(dba)_3$ (1.5 mol%), P(*t*Bu)$_3$.HBF$_4$ (3.6 mol%) and KF (3.3 equiv.). [c]$Pd(OAc)_2$ (2 mol%), DavePhos (3 mol%) and CsF (3.0 equiv.). [d]10 mol%.

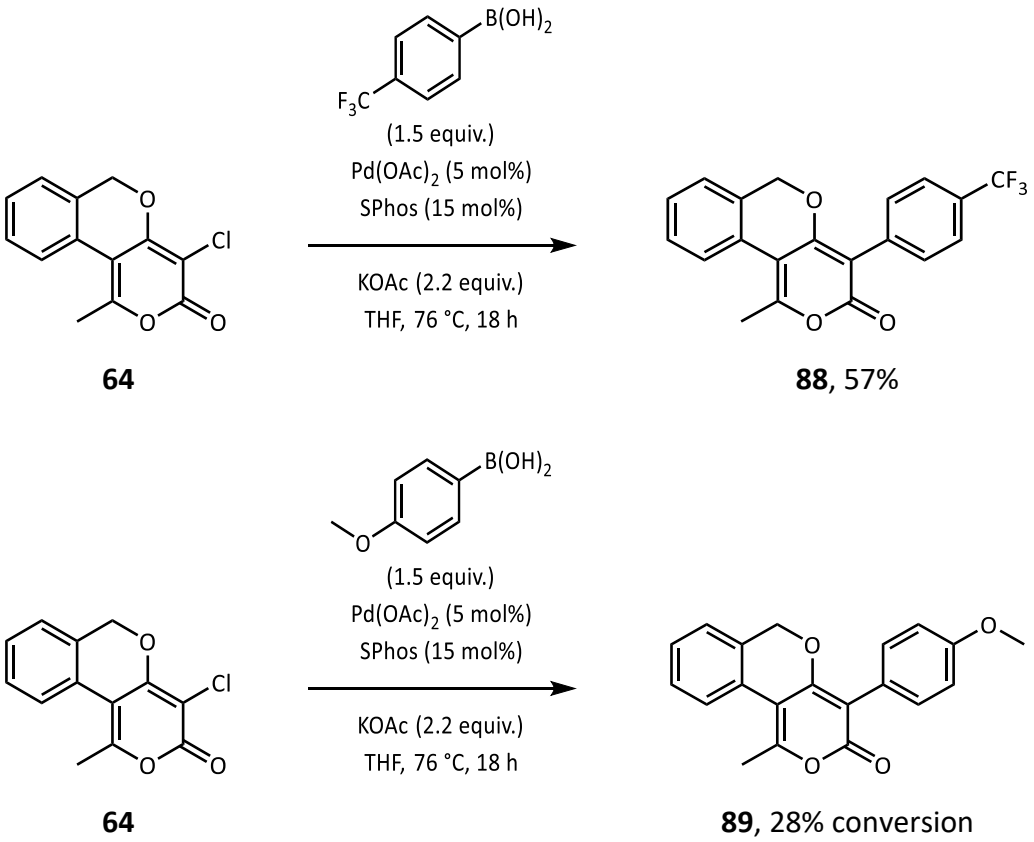
Disappointingly, conditions such as those reported by Fu (**Table 3.2**, **entry 1**)[19] and Buchwald (**Table 3.2**, **entry 2**)[20] for the cross-coupling of aryl chlorides failed to give the desired product.

Crucially, upon consideration of the ^{13}C NMR spectrum of **64**, it became apparent that the C–3–Cl bond (^{13}C at δ = 100.8 ppm) did not necessarily possess the

characteristics of an aryl chloride bond (expect ^{13}C at δ ~ 130 ppm). Therefore, the conditions reported by Hultin for the Suzuki-Miyaura cross-coupling of an α-chloro-α,β-unsaturated ester were tested (**Table 3.2**, **entry 3**).[21] Pleasingly, similar conditions gave 60% conversion to the desired product **87**. Using KOAc as base (**Table 3.2**, **entry 4**), gave a slightly increased conversion (to 70%). Using 2-MeTHF (**Table 3.2**, **entry 5**) and 1,4-dioxane (**Table 3.2**, **entry 6**) as solvents, did not help to promote the reaction. Changing to a Pd(0) source in THF, surprisingly, led to poor catalytic turnover of 6% (**Table 3.2**, **entry 7**). Bulky, electron-rich ligands are reported to be efficient for the coupling of aryl chlorides due to their proclivity to donate electron density to the intermediate Pd(0) complex to facilitate oxidative addition.[22] SPhos has the capacity to stabilise a monoligated Pd(0) centre by interaction between Pd and the *ipso*-carbon of the lower ring, and also to stabilise a Pd(II) center by coordination of the alkoxy group to Pd. This combination results in highly reactive catalysts that are also rather stable.[23] RuPhos (**Table 3.2**, **entry 8**) possesses similar structural features to SPhos but was not as effective for this transformation. It would seem that increasing the steric bulk using XPhos (**Table 3.2**, **entry 9**) has a detrimental effect on conversion. Finally, the optimal conditions were found using $Pd(OAc)_2$ and SPhos with KOAc in refluxing THF (**Table 3.2**, **entry 10**). These conditions gave 93% conversion and an excellent isolated yield of 92%.

3.2.2. Substrate effects on Suzuki-Miyaura cross-coupling

To test the effect of varying the electronics of the phenylboronic acid, two other phenylboronic acids were tested (**Scheme 3.2**).



Scheme 3.2. Substrate scope for the Suzuki-Miyaura coupling reaction.

An electron-poor *p*-trifluoromethylphenylboronic acid was first employed in the reaction. This provided the expected product **88** in 57% isolated yield. However, electron-rich *p*-methoxyphenylboronic acid gave only 28% conversion to **89**. This indicates that electron-rich boronic acids may not be well tolerated by these reactions conditions.

3.2.3. Conclusions

A synthetic methodology was developed allowing access to previously inaccessible 'cyclised-at-C5' 2-pyrones and 2-pyridones (**Section 2.3**). Further elaboration at C–3 was enabled utilising the retained C–Cl bond in a Suzuki-Miyaura cross-coupling. This shows that while the C–Cl bond at the C–3 of the 2-pyrone framework is stable

enough to withstand the conditions of a direct arylation reaction, it remains reactive enough to participate in Suzuki-Miyaura cross-coupling. This methodology allows the synthesis of highly decorated 2-pyrone compounds.

3.3. A greener approach to chlorination and Suzuki-Miyaura cross-coupling

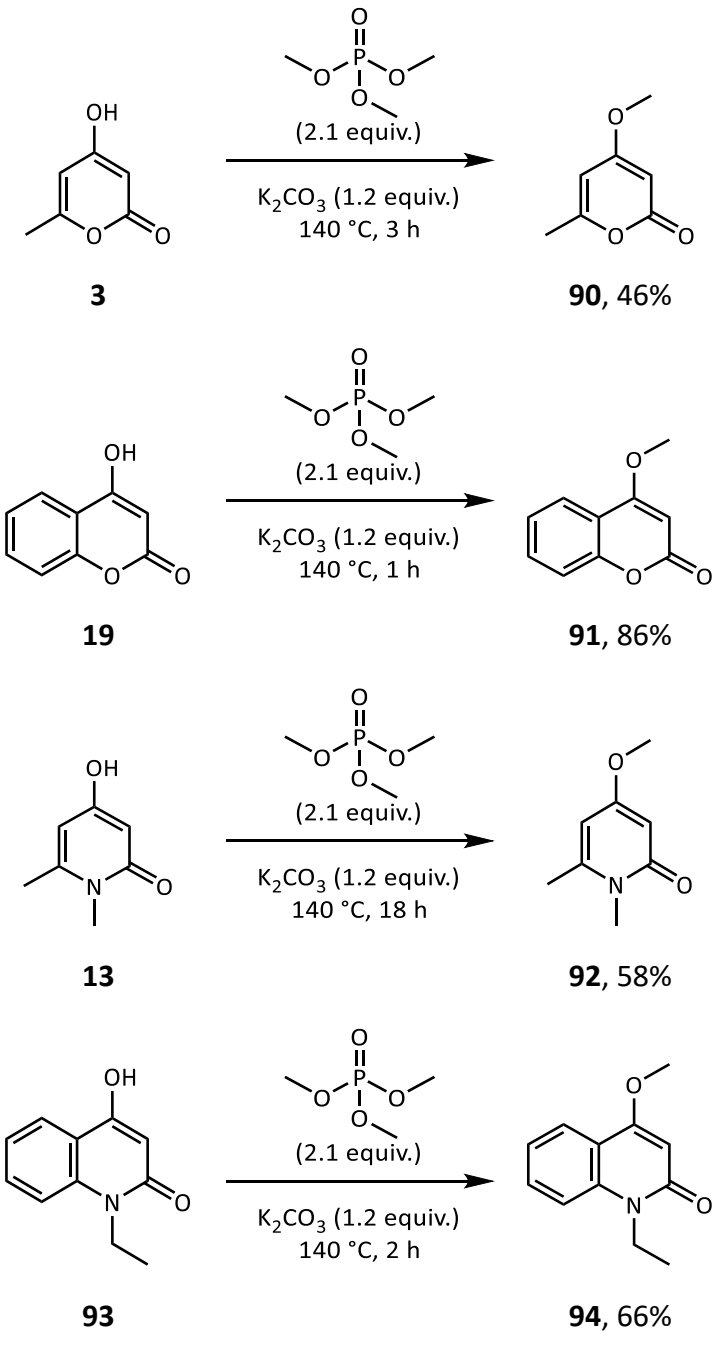
In modern synthetic chemistry, it is important achieve a successful chemical reaction in an efficient and sustainable way. In particular, top pharmaceutical companies are seeking reactions which are executed in non-chlorinated solvents.[24-25] More generally applicable, environmentally friendly cross-coupling conditions were sought to allow the application of these principles to the Suzuki-Miyaura cross-coupling of 2-coumarins. As previously discussed in **Chapter 1**, 2-coumarins display a remarkable biological profile including anti-cancer, anti-microbial, anti-inflammatory, anti-thrombotic and anti-psychotic effects.[26-27]

Previous work on Suzuki-Miyaura reactions at the C–3 position of 4-alkoxy-2-coumarins has involved bromides.[28] Suzuki-Miyaura reactions involving a chloride at the C–3 position of 2-coumarins have been reported for 4-hydro-[29] and 4-alkyl-2-coumarins,[30] however, we have observed that the electronic changes caused by introducing 4-alkoxy groups can cause these reported conditions to fail. For example, the conditions described by Degorce *et al.*[30] required the use of a bromide to achieve good yields when 4-alkoxy-2-coumarins were used. Application of the dioxane/water conditions described by Degorce *et al.*[30] for a 3-chloro-4-alkyl-2-coumarin gave a 43% yield of product **115**, compared to 88% under our conditions. These yields were determined from the ^{1}H NMR spectrum of the crude reaction mixture, using 1,3,5-trimethoxybenzene as the internal standard for quantification.

3.3.1. Synthesis of starting materials

It was decided to use 4-methoxy derivatives of 2-pyrone, 2-pyridone, 2-coumarin and 2-quinolone as model substrates for the Suzuki-Miyaura cross-coupling because they are readily accessible. Additionally, 4-alkoxy derivatives of 2-pyrones, in particular, have been shown to possess a variety of biological effects.[31] The 4-methoxy substrates were prepared by reaction of the 4-hydroxy derivative with trimethylphosphate in the presence of K_2CO_3 (**Scheme 3.3**). Trimethylphosphate is a mild methylating agent with a low acute toxicity (LD_{50} rats 2 g/kg[32]).[33] 4-Hydroxy-6-methyl-2-pyrone (**3**) and 4-hydroxy-2-coumarin (**19**) were commercially available.

4-Hydroxy-1,6-dimethyl-2-pyridone (**13**) was prepared as described in **Section 2.2.1**. 4-Hydroxy-1-ethyl-2-quinolone (**93**) was obtained from another member of the McGlacken group.[34]



3 **90**, 46%

19 **91**, 86%

13 **92**, 58%

93 **94**, 66%

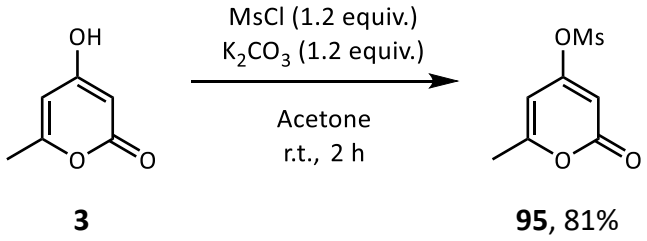
Scheme 3.3. Methylation of 4-hydroxy starting materials.

The methylation of 4-hydroxy-2-pyrone **3** went to completion in 3 h, and the 4-methoxy product **90** was isolated in 46% yield after recrystallisation from EtOH. The characteristic methoxy 3H singlet at 3.80 ppm in the ^{1}H NMR spectrum, and at

55.8 ppm in the ^{13}C NMR spectrum indicated the success of the transformation. Similarly, 4-hydroxy-2-coumarin (**19**) was methylated to give product **91** in 86% yield after just 1 h. The methylated 2-pyridone **92** and 2-quinolone **94** were prepared in 58% and 66% isolated yields respectively.

To examine the effect of different 4-alkoxy groups on the Suzuki-Miyaura reaction (see **Section 3.3.2** and **Section 3.3.3**), a variety of alkylated 2-pyrones and 2-coumarins were synthesised.

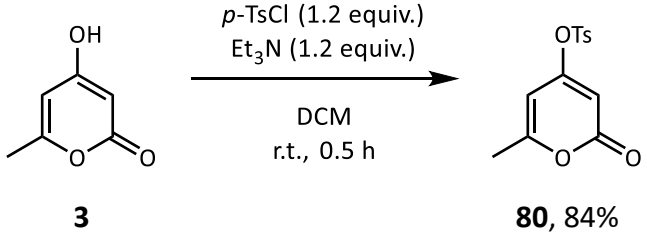
4-Mesyloxy-2-pyrone **95** was synthesised as shown in **Scheme 3.4**. 4-Hydroxy-6-methyl-2-pyrone (**3**) was deprotonated by K_2CO_3 at ambient temperature. Mesyl chloride was then added, and the reaction mixture was stirred at ambient temperature for 2 h. The crude product was purified by recrystallisation from EtOH to give **95** in 81% yield.



3 **95**, 81%

Scheme 3.4. Mesylation of 4-hydroxy-2-pyrone **3**.

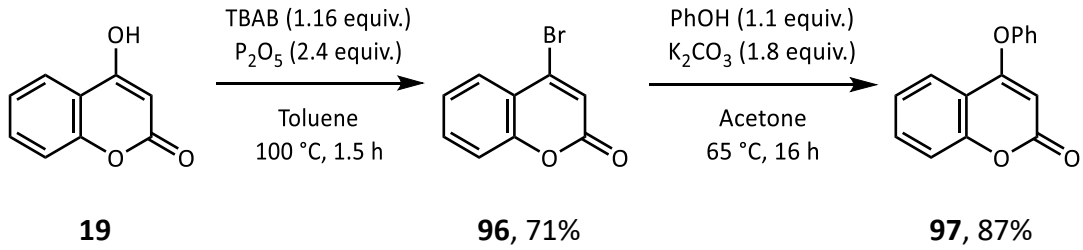
4-Tosyloxy-2-pyrone **80** was synthesised as shown in **Scheme 3.5**. 4-Hydroxy-6-methyl-2-pyrone (**3**) was deprotonated by Et_3N at ambient temperature. *p*-Tosyl chloride was then added, and the reaction mixture was stirred at ambient temperature for 0.5 h. The crude product was purified by recrystallisation from a mixture of DCM/hexanes to give **80** in 84% yield.



3 **80**, 84%

Scheme 3.5. Tosylation of 4-hydroxy-2-pyrone **3.**

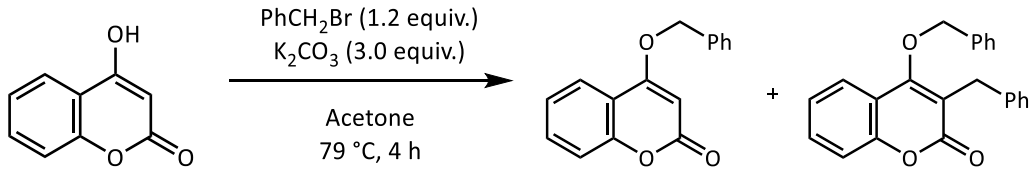
4-Phenoxy-2-coumarin (**97**) was synthesised as shown in **Scheme 3.6**. 4-Hydroxy-2-coumarin **19** was brominated by TBAB in the presence of P_2O_5 to give 4-bromo-2-coumarin **96** in 71% yield, which was then coupled with phenol in the presence of K_2CO_3 to give the product **97** in 87% yield.



19 **96**, 71% **97**, 87%

Scheme 3.6. Synthesis of 4-phenoxy-2-coumarin **97**.

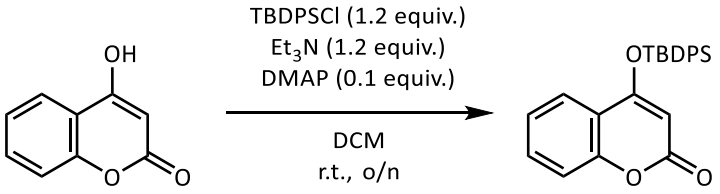
4-Hydroxy-2-coumarin (**19**) was deprotonated with K_2CO_3 and treated with benzyl bromide to give 4-benzyloxy-2-coumarin (**98**) in 19% yield after column chromatography on silica gel (**Scheme 3.7**). Difficulties were encountered in the purification of the product due to the presence of a dibenzylated side-product **99**, in a similar manner to that discussed in **Section 2.2.1**.



19 **98**, 19% **99**

Scheme 3.7. Benzylation of 4-hydroxy-2-coumarin **19**.

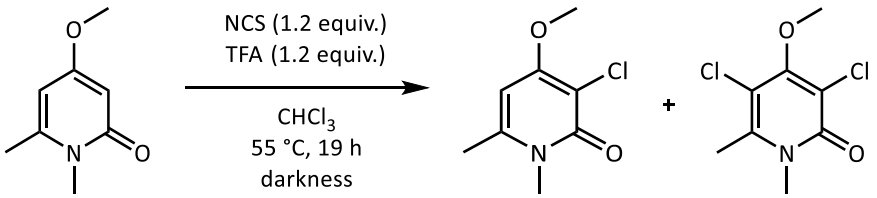
A 2-coumarin substrate bearing a silyl ether protecting group was also synthesised (**Scheme 3.8**). 4-Hydroxy-2-coumarin (**19**) reacted with *t*-butyldiphenylsilyl chloride (TBDPSCl) in the presence of Et_3N. The crude reaction mixture was subjected to column chromatography on silica gel using 10:90 EtOAc:hexanes as the eluent. The product was further purified by recrystallisation from EtOH to give **100** in 54% yield.



19 **100**, 54%

Scheme 3.8. Silyl ether protection of 4-hydroxy-2-coumarin **19.**

The next step towards preparing the desired substrates required selective chlorination of the C–3 position of the 4-methoxy substrates. 2-Pyridone **92** was chlorinated using *N*-chlorosuccinimide (NCS) in the presence of trifluoroacetic acid (TFA) (**Scheme 3.9**).



92 **101**, 30% **102**

Scheme 3.9. Chlorination of 2-pyridone **92**.

Using these conditions, mono-chlorination of 2-pyridone **92** was the major product. However, 3,5-dichlorination was also observed to give **102**. A nominal mass spectrum of the crude reaction mixture showed molecular ions corresponding to both mono- and di-chlorination. The formation of **102** could not be prevented, as it was present as a side-product even when there was residual starting material still present, as can be seen in the ^{1}H NMR spectrum of the crude reaction mixture (**Figure 3.1**). The crude reaction mixture containing both the mono- and di-chlorinated products was subjected to column chromatography on silica gel using DCM as the eluent. The fractions containing the mono-chlorinated product were concentrated under reduced pressure and recrystallised from EtOH to give **101** in 30% yield. A pure sample of the di-chlorinated product could not be obtained. However, an impure sample was isolated which allowed the identification of the important ^{1}H NMR signals.

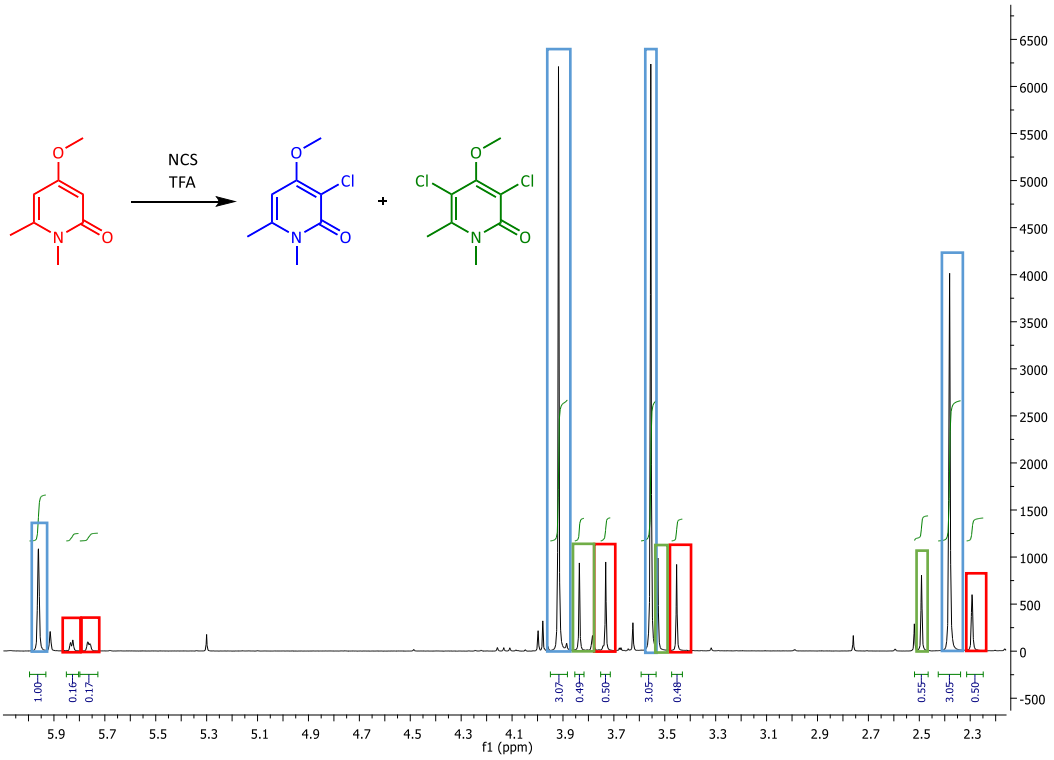
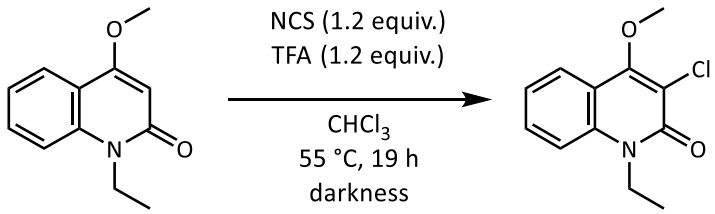


Figure 3.1. ^{1}H NMR spectrum of the crude reaction mixture for the chlorination of 2-pyridone **92.**

2-Quinolone **94** was also chlorinated using NCS in the presence of TFA to give **103** in 68% yield after column chromatography on silica gel (**Scheme 3.10**).

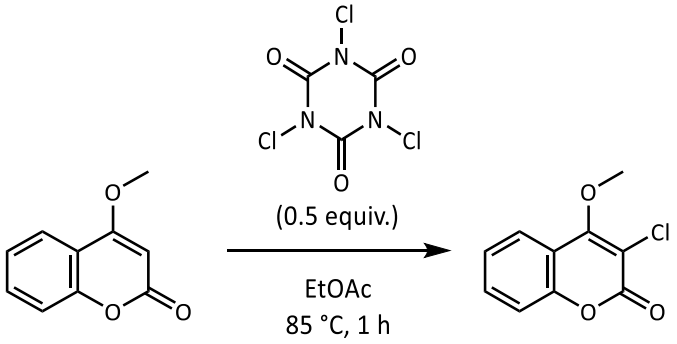


94 **103**, 68%

Scheme 3.10. Chlorination of 2-quinolone **94**.

3.3.2. Chlorination with trichloroisocyanuric acid

While NCS is the reagent of choice in many cases for introducing chloride to heteroaromatic compounds, trichloroisocyanuric acid (TCCA) is more atom-economic, more soluble, less toxic and cheaper.[35] 2-Coumarin **91** was chlorinated by reaction with TCCA in refluxing EtOAc for 1 h to give the product **104** (**Scheme 3.11**).



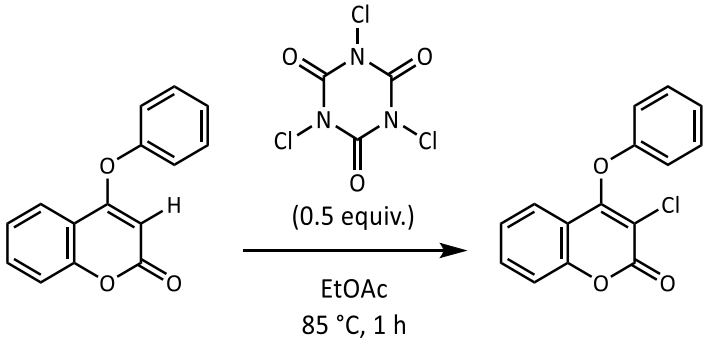
91 **104**, 58%

Scheme 3.11. Chlorination of 4-methoxy-2-coumarin **91** with TCCA.

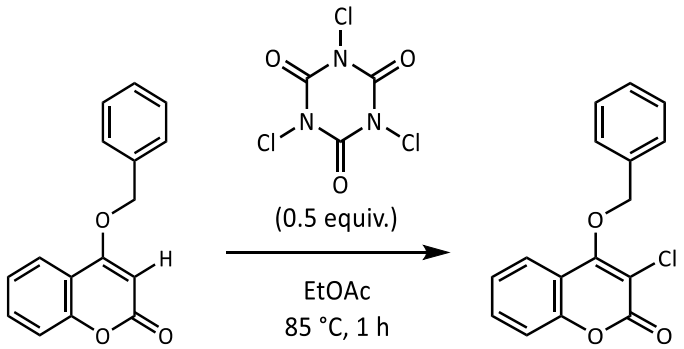
While TCCA is soluble in the reaction mixture, the by-product cyanuric acid is largely insoluble. Thus the products can be purified *via* a simple filtration, followed by recrystallisation of the concentrated filtrate from EtOH. The appearance of cyanuric acid in the reaction mixture is a useful indicator that the reaction is progressing, as the mixture goes from a clear solution to a cloudy suspension when cyanuric acid forms.

Compound **104** is known to have formed when the 1H signal at 5.70 ppm corresponding to the C–3 proton of **91** is no longer present in the ^{1}H NMR spectrum of the crude reaction mixture. Also, the appearance of a quaternary carbon signal at 106.0 ppm in the ^{13}C NMR spectrum is attributed to the C–3 position of **104**. The mass spectrum shows that the molecular ions of 211 (^{35}Cl) and 213 (^{37}Cl) g mol^{-1} are present in a 3:1 ratio, which is indicative of the presence of a chlorine atom in the molecule.

The use of TCCA to chlorinate 2-coumarins represents a significant improvement in efficiency over the previously reported conditions.[36] For example, 2-coumarin **105** was previously synthesised in 67% isolated yield after 72 h at 55 °C using a combination of NCS and TFA.[36] In this case, using TCCA, **105** can be produced in 64% isolated yield after 1 h at 85 °C in EtOAc (**Scheme 3.12**). Benzylated 2-coumarin **98** was also successfully chlorinated to give **106** in 1 h in 67% isolated yield (**Scheme 3.12**).



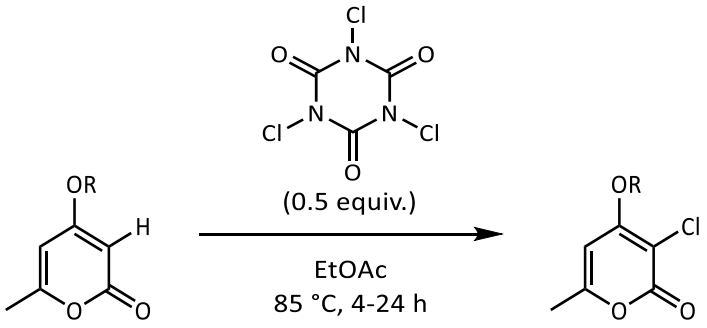
97 **105**, 64%



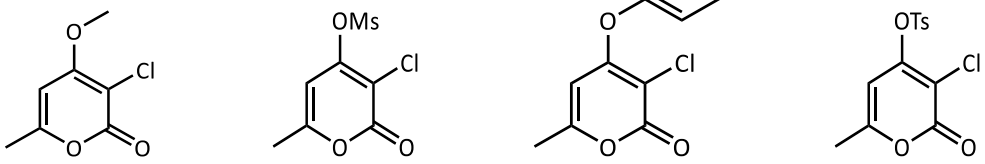
98 **106**, 67%

Scheme 3.12. Chlorination of 2-coumarins with TCCA.

This procedure can be extended to the related 2-pyrone framework (**Scheme 3.13**). 2-Pyrones are a less robust substrate than the corresponding 2-coumarins, which may explain the lower yields. It is pleasing, however, that chlorination proceeds cleanly, even in the presence of mesyl (**95**) and tosyl (**80**) groups in the starting materials.



107-**110**



107, 57%
4 h

108, 31%
24 h

109, 27%
6 h

110, 40%
24 h

Scheme 3.13. Chlorination of 2-pyrones.

Attempts to use the TCCA conditions to chlorinate 2-pyridone **92** and 2-quinolone **94** led to inseparable mixtures of products, even at lower temperatures. Hence, the NCS/TFA conditions (**Scheme 3.9** and **Scheme 3.10**) were used to access substrates **101** and **103**.

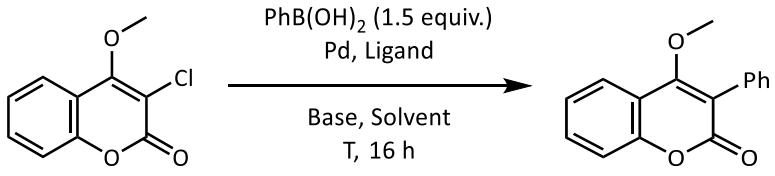
3.3.3. Suzuki-Miyaura cross-coupling of 3-chloro-2-coumarins

With the desired 3-chloro-2-coumarin **104** in hand, reaction conditions were sought which would allow the Suzuki-Miyaura reaction to occur at this challenging site. Using SPhos as a ligand had previously been successful for the Suzuki-Miyaura coupling of 3-chloro-2-pyrones (**Section 3.2.1**), so this formed the basis of the decision to use SPhos as the ligand for the cross-coupling reaction of 3-chloro-2-coumarins (**Table 3.3**).

The Innovative Medicines Initiative (IMI)-CHEM21 public-private partnership is a European consortium which comprises of pharmaceutical companies, universities and small to medium enterprises which promotes sustainable biological and chemical methodologies. A solvent selection guide published by this consortium was

used to limit our solvent choices to greener options during the development of reaction conditions.[25]

Table 3.3. Optimisation of Suzuki-Miyaura reaction conditions.



104 **111**

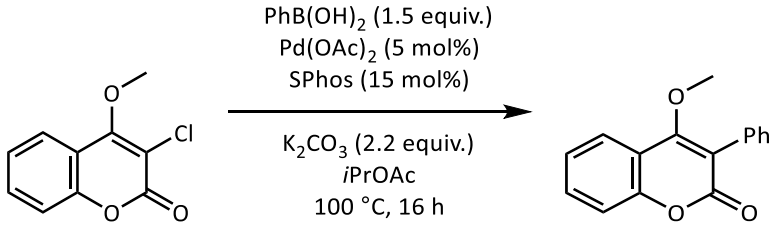
Entry	Pd (5 mol%)	Ligand (15 mol%)	Base (2.2 equiv.)	Solvent	T (°C)	Conv. (%)	Yield[a] (%)
1	$Pd(OAc)_2$	SPhos	Na_2CO_3	EtOH	90	100	22[b]
2	$Pd(OAc)_2$	SPhos	Na_2CO_3	2-MeTHF	90	63	54
3	$Pd(OAc)_2$	SPhos	Na_2CO_3	*i*PrOAc	100	97	80
4	$Pd_2(dba)_3$	SPhos	Na_2CO_3	*i*PrOAc	100	90	70
5	$Pd(OAc)_2$	RuPhos	Na_2CO_3	*i*PrOAc	100	100	80
6	$Pd(OAc)_2$	PPh_3	Na_2CO_3	*i*PrOAc	100	14	12
7	$Pd(OAc)_2$	SPhos	KOAc	*i*PrOAc	100	36	29
8	$Pd(OAc)_2$	SPhos	K_2CO_3	*i*PrOAc	100	100	84 (82)

[a] Yields were determined using ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as the internal standard for quantification. Isolated yields in parenthesis. [b]A 45% yield (by internal standard) of dechlorinated side-product **91** was also identified in the ^{1}H NMR spectrum of the crude reaction mixture.

The use of EtOH as solvent (**Table 3.3**, **entry 1**) allowed the full consumption of starting material **104**, with a 22% yield of desired product **111** along with a 45% yield of dechlorinated side-product **91**. Switching to an aprotic polar solvent, 2-methyltetrahydrofuran (2-MeTHF) gave a 54% yield of the desired product without significant dechlorination (**Table 3.3**, **entry 2**). The optimal solvent was determined to be isopropyl acetate (*i*PrOAc) which gave **111** in 80% yield (**Table 3.3**, **entry 3**). Changing to a palladium(0) source reduced the yield (**Table 1**, **entry 4**), while

changing to the RuPhos ligand (**Table 3.3**, **entry 5**) offered no advantages over SPhos, and PPh_3 (**Table 3.3**, **entry 6**) gave a poor 12% yield. Employing KOAc as base hindered the reaction (**Table 3.3**, **entry 7**). The best conditions for the transformation were found when K_2CO_3 was used as the base, which gave 100% conversion to the desired product **111** in 82% isolated yield (**Table 3.3**, **entry 8**).

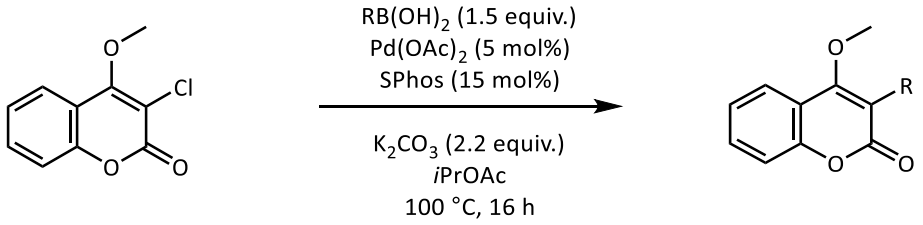
To further demonstrate the utility and practicality of these conditions, the Suzuki-Miyaura cross-coupling of **104** with phenylboronic acid was performed on a gram-scale, giving **111** in an isolated yield of 84% (1.0 g) without chromatography. This constitutes a successful 20-fold scale-up from the demonstrated reaction conditions, and no loss of yield is observed (**Scheme 3.14**).



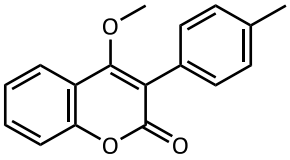
104 **111**, 84% (1.0 g)

Scheme 3.14. Scale-up of optimised Suzuki-Miyaura conditions.

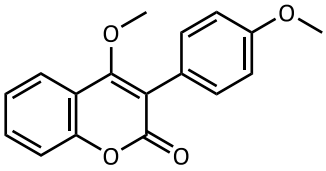
With the optimised conditions in hand, we sought to demonstrate the variety of substituted phenylboronic acids which were tolerated by our reaction conditions. A range of *para*-substituted phenylboronic acids were tested (**Scheme 3.15**), and no significant electronic effects were observed. *p*-Methoxyphenylboronic acid gave **113** in 79% yield, while *p*-(trifluoromethyl)phenylboronic acid gave **114** in 76% yield. Sensitive functional groups such as aldehydes and esters also survived the coupling conditions, and products **117** and **118** were isolated in 48% and 91% yield respectively. 4-Styrylboronic acid coupled to give **121** in 77% isolated yield, with the alkenyl functionality remaining untouched, demonstrating some chemoselectivity over the potentially competitive Heck reaction. Substituents which could potentially ligate to Pd and inhibit the reaction were also well-tolerated, giving products such as nitrile **120** (**Scheme 3.15**), primary amine **122** and the nitro **124** (**Scheme 3.16**) in good yields.



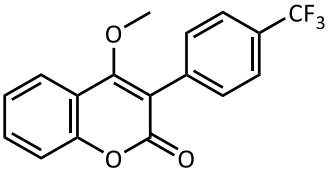
104 **112-121**



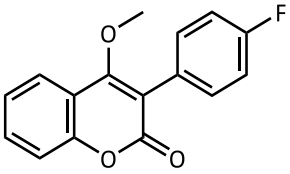
112, 89%



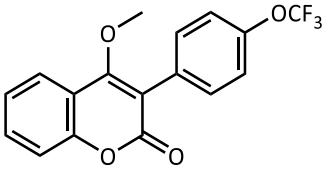
113, 79%



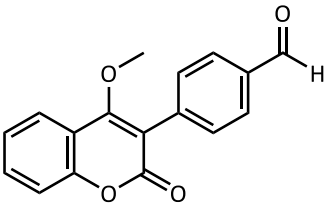
114, 76%



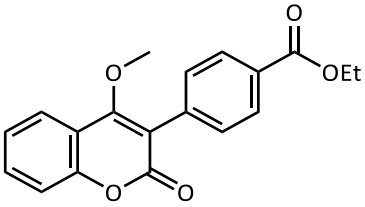
115, 72%



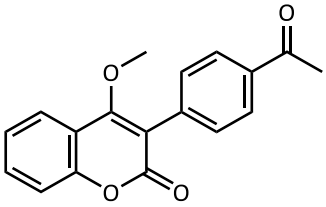
116, 77%



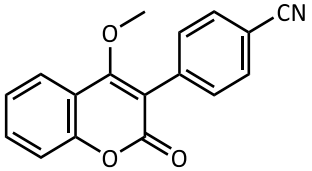
117, 48%



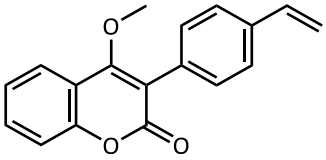
118, 91%



119, 76%



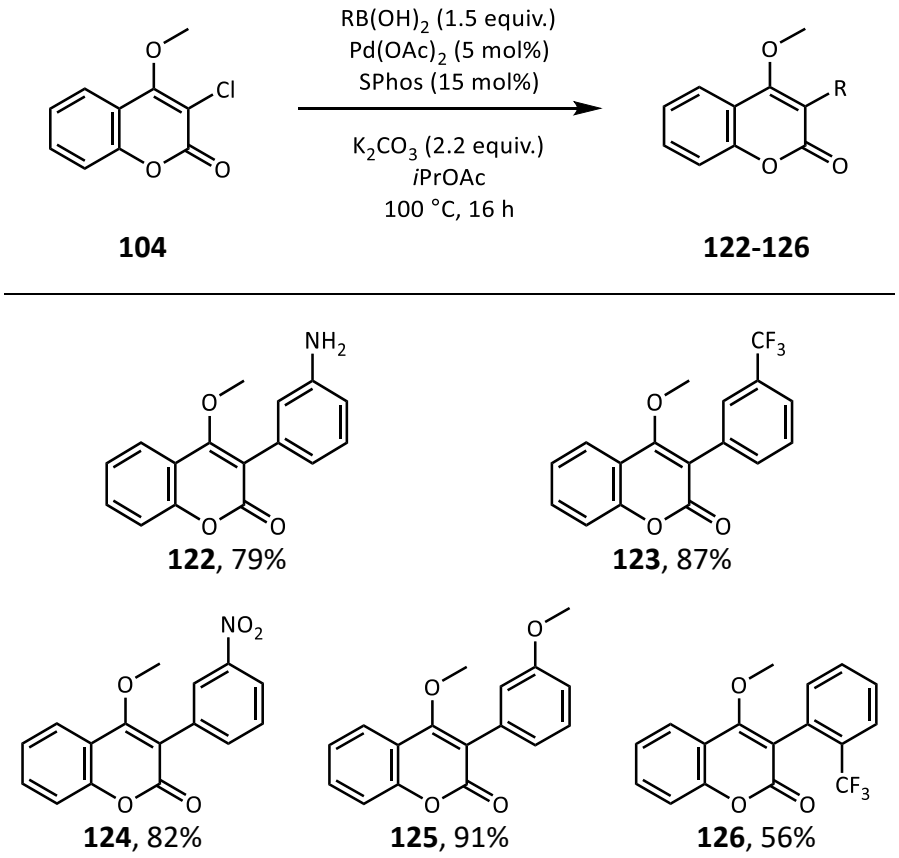
120, 84%



121, 77%

Scheme 3.15. Variety of *para*-substituted phenylboronic acids tolerated under Suzuki-Miyaura reaction conditions.

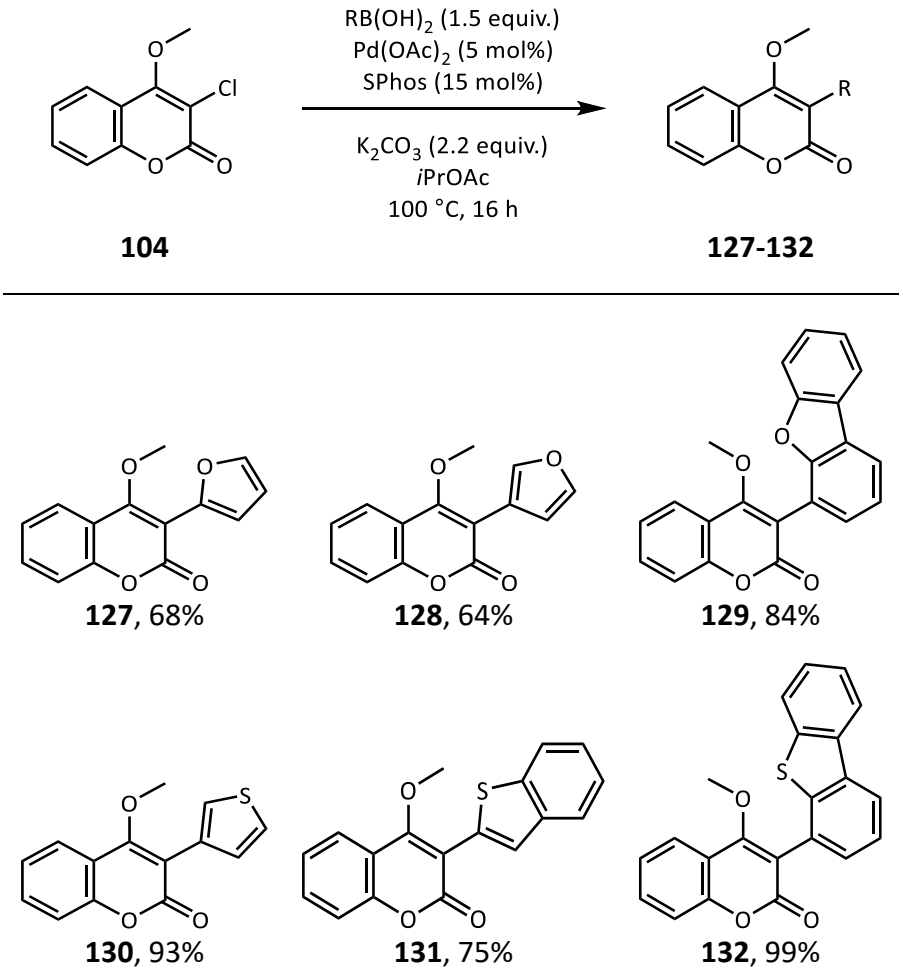
meta-Substituted phenylboronic acids gave higher yields than the corresponding *para*-substituted phenylboronic acids (**Scheme 3.16**), *e.g. m*-methoxyphenylboronic acid gave **125** in 91% yield. A somewhat sterically hindered *ortho*-substituted phenylboronic acid also coupled to give **126** in 56% yield.



Scheme 3.16. Variety of *meta* and *ortho*-substituted phenylboronic acids tolerated under Suzuki-Miyaura reaction conditions.

The presence of other halides, such as with *p*-bromo- or *p*-chlorophenylboronic acids, resulted in multiple side reactions, potentially including polymerisation to give inseparable mixtures of products. An alkenyl boronic acid, (4-methylstyryl)boronic acid, failed to participate in the Suzuki-Miyaura coupling, as did the alkyl boronic acids, isobutylboronic acid and *n*-propylboronic acid.

Having achieved success with a wide range of substituted phenylboronic acids, we turned our attention towards more challenging heteroaryl boronic acids (**Scheme 3.17**).

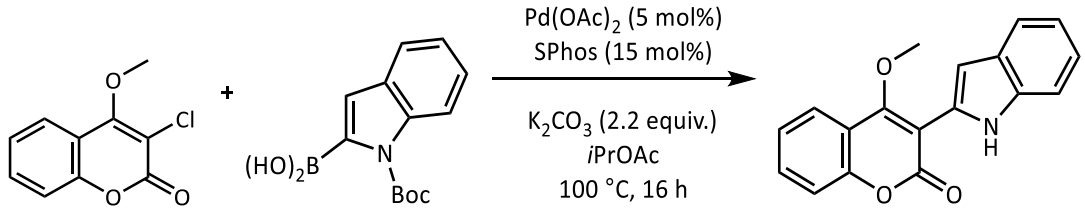


Scheme 3.17. Variety of heteroaryl boronic acids tolerated under the reaction conditions.

In Buchwald and co-workers systematic study on the powerful reactivity of SPhos, 2-furanyl boronic acid failed to react efficiently with unactivated aryl chlorides.[37] Pleasingly, under our conditions 2- and 3-furanylboronic acids coupled successfully to give **127** and **128** in 68% and 64% yield respectively. The 3-thiopheneboronic acid gave **130** in 93% isolated yield. 2-Benzothiophene **131**, dibenzofuran **129** and dibenzothiophene **132** groups were introduced at the 3-position using the standard conditions to give the Suzuki-Miyaura products in good to excellent yields. The highest yield for this study was obtained for product **132** in 99% yield. A 2-thiopheneboronic acid and a 2-benzofuran boronic acid failed to participate in Suzuki-Miyaura coupling with **104**. This is somewhat surprising given the success of the 2-furanyl and 2-benzothiophene boronic acids. However, 2-heterocyclic boronic acids are known to decompose in air *via* protodeboronation, oxidation, and/or

polymerisation.[38] Such pathways are thought to be accelerated in the presence of heat, base, and/or a Pd catalyst, causing the *in situ* decomposition of unstable boronic acids to compete with their cross-coupling.[38] In couplings with slower reacting halides, such as unactivated aryl chlorides, the latter challenge is exacerbated. This could explain the failure of the aforementioned boronic acids to couple under the presented conditions. Pyridylboronic acids or esters were also not tolerated, which is likely to be caused by interaction of Pd with the strongly coordinating lone pair of electrons on the pyridyl nitrogen.

Additionally, a Boc-protected indole boronic acid successfully underwent the Suzuki-Miyaura cross-coupling (**Scheme 3.18**).



104 (1.5 equiv.) **133** 55%

Scheme 3.18. Successful Suzuki-Miyaura cross-coupling with an indole boronic acid.

The Boc group was cleaved *in situ*, likely by one of the acid sources in the reaction, to give **133** as the main product of the reaction in 55% isolated yield.

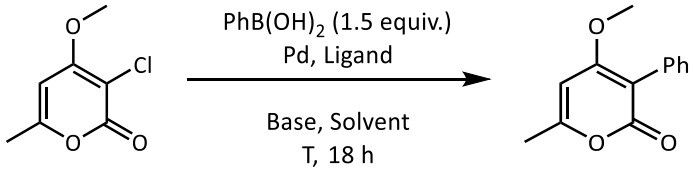
3.3.4. Suzuki-Miyaura cross-coupling of related 3-chloro heterocycles

Given the diverse range of both aryl and heteroaryl boronic acids which are tolerated by these reaction conditions, we questioned whether the conditions might also be general for the structurally-related 3-chloro-2-pyrone, -pyridone and -quinolone. These heterocycles, while structurally-related, are chemically diverse. The nitrogen of the 2-quinolone could potentially ligate to Pd, inhibiting the reaction, while 2-pyrones and 2-pyridones are suspected to be less aromatic in character than the corresponding 2-coumarins and 2-quinolones. 2-Pyrones in particular have been demonstrated to have a rich variety of chemical properties and can behave like aromatics,[39] dienes[40-41] and enones.[42] Moreover, the framework can ring-open under

certain cross-coupling conditions.[43] Thus, 2-pyrones in particular, present significant chemoselectivity challenges.

An optimisation study was conducted to investigate whether the conditions which gave successful Suzuki-Miyaura coupling of 2-coumarin **104** would also be applicable to 2-pyrone **107** (**Table 3.4**).

Table 3.4. Suzuki-Miyaura coupling of 2-pyrone **107**.



107 **134**

Entry	Pd (5 mol%)	Ligand (15 mol%)	Base (2.2 equiv.)	Solvent	T (°C)	Conv. (%)[a]
1	$Pd(OAc)_2$	SPhos	KOAc	THF	76	9
2	$Pd(OAc)_2$	SPhos	KOAc	2-MeTHF	90	3
3	$Pd(OAc)_2$	SPhos	KOAc	EtOAc	85	5
4	$Pd(OAc)_2$	SPhos	KOAc	MEK	90	2
5	$Pd(OAc)_2$	SPhos	KOAc	EtOH	90	11
6	$Pd(OAc)_2$	SPhos	KOAc	*i*PrOH	90	4
7	$Pd(OAc)_2$	SPhos	KOAc	*n*BuOAc	100	41
8	$Pd(OAc)_2$	SPhos	KOAc	*i*PrOAc	100	45
9	$Pd(OAc)_2$	SPhos	Na_2CO_3	*i*PrOAc	100	95
10[b]	$Pd(OAc)_2$	SPhos	Na_2CO_3	*i*PrOAc	100	76
11	$Pd(OAc)_2$	SPhos	Na_2CO_3	*i*PrOAc	70	33
12	$Pd(OAc)_2$	SPhos	Na_2CO_3	*i*PrOAc	50	5
13	$Pd(OAc)_2$	SPhos	Na_2CO_3	*i*PrOAc	25	0
14	$Pd(CH_3CN)_2Cl_2$	SPhos	Na_2CO_3	*i*PrOAc	100	59
15	$Pd(NH_3)_4SO_4$	SPhos	Na_2CO_3	*i*PrOAc	100	2
16	$Pd_2(dba)_3$	SPhos	Na_2CO_3	*i*PrOAc	100	22
17	$Pd(OPiv)_2$	SPhos	Na_2CO_3	*i*PrOAc	100	7

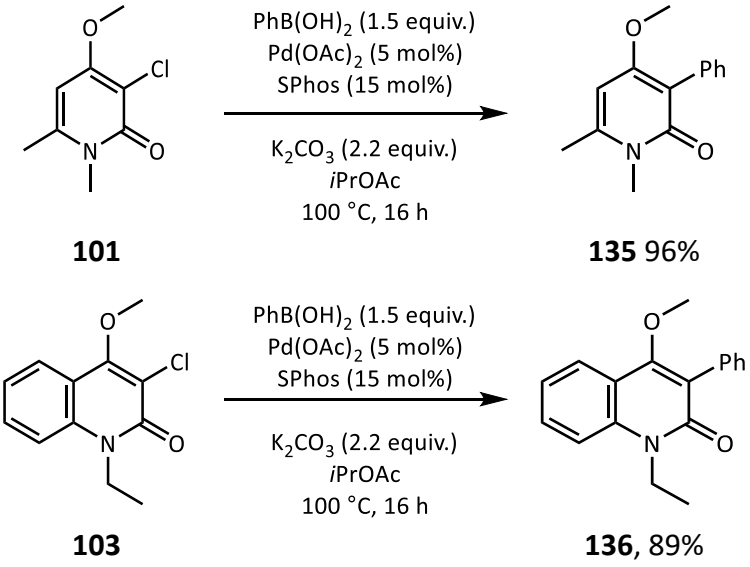
18	$Pd(OAc)_2$	RuPhos	Na_2CO_3	*i*PrOAc	100	78
19	$Pd(OAc)_2$	MePhos	Na_2CO_3	*i*PrOAc	100	14
20	$Pd(OAc)_2$	DavePhos	Na_2CO_3	*i*PrOAc	100	24
21	$Pd(OAc)_2$	XPhos	Na_2CO_3	*i*PrOAc	100	21
22	$Pd(OAc)_2$	P(*t*Bu)$_3$	Na_2CO_3	*i*PrOAc	100	0
23	$Pd(OAc)_2$	PCy_3	Na_2CO_3	*i*PrOAc	100	9
24	$Pd(OAc)_2$	PPh_3	Na_2CO_3	*i*PrOAc	100	0
25	$Pd(OAc)_2$	SPhos	K_2CO_3	*i*PrOAc	100	96 (75)

[a]Conversion calculated as the ratio of starting material to product in the ^{1}H NMR spectrum of the crude reaction mixture. Isolated yields in parenthesis. [b]2 mol% $Pd(OAc)_2$ and 6 mol% SPhos were used.

The first set of conditions tested were those that had proven successful for the Suzuki-Miyaura coupling of 2-pyrone **64** (**Table 3.4**, **entry 1**). Solvent selection was again limited by a solvent selection guide.[25] Of the solvents tested (**Table 3.4**, **entry 2-8**), *i*PrOAc (**Table 3.4**, **entry 8**) gave the best result and was carried forward. Switching to a carbonate base (**Table 3.4**, **entry 9**) greatly improved the conversion to the desired product **134**. Reduced Pd loading (**Table 3.4**, **entry 10**) and lower temperatures (**Table 3.4**, **entry 11-13**) were not conducive to successful coupling. A range of alternative Pd sources were tested (**Table 3.4**, **entry 14-17**), but none gave better results than $Pd(OAc)_2$. RuPhos performed similarly well in the presence of Na_2CO_3 (**Table 3.4**, **entry 18**), but all other phosphine ligands screened were less successful than SPhos (**Table 3.4**, **entry 19-24**). Finally, a stronger carbonate base, K_2CO_3 (**Table 3.4**, **entry 25**), was employed in the reaction, which gave an excellent conversion of 96%, and 75% isolated yield of **134**. This shows that the optimal conditions for reaction with 2-coumarin **104** (**Table 3.3**, **Entry 8**) also gave the best result for 2-pyrone **107** (**Table 3.4**, **entry 25**).

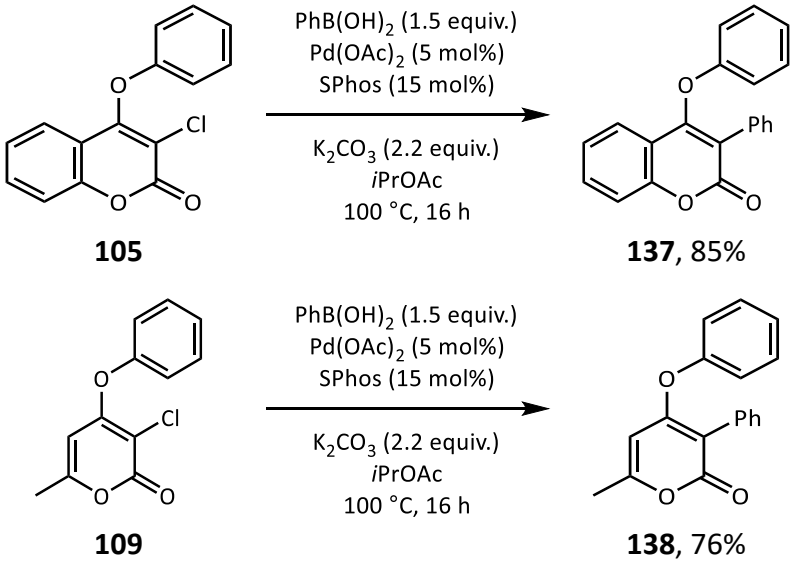
2-Pyridone **101** and 2-quinolone **103** were also coupled in excellent yields, and **135** and **136** were isolated in 96% and 89% yields respectively (**Scheme 3.19**). As far as we are aware, this is the first time that Suzuki-Miyaura conditions optimised for one

of these heterocyclic substrates has been demonstrated to be general across 2-coumarins, 2-pyrones, 2-pyridones and 2-quinolones.



Scheme 3.19. Suzuki-Miyaura cross-coupling of 2-pyridone **101** and 2-quinolone **103**.

Next, we tested the effect of varying the 4-alkoxy group. The 4-phenoxy group can prove more sterically demanding than the 4-methoxy group, and yet it did not hinder the progress of the reaction (**Scheme 3.20**).

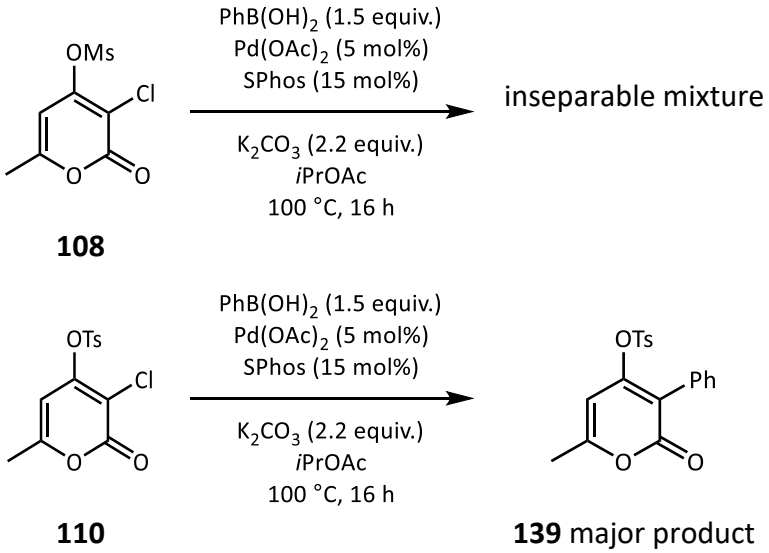


Scheme 3.20. Variation of the 4-OR group in the Suzuki-Miyaura cross-coupling.

Compounds **105** and **109** were coupled with phenylboronic acid to give **137** and **138** in 85% and 76% yields respectively. It is particularly interesting that no products as a

result of an intramolecular direct arylation process[36] were observed in the ^{1}H NMR spectrum of the crude reaction mixture.

Unfortunately, attempts to couple **108** and **110** with phenylboronic acid gave mixtures of mono- and di-arylated products, along with other unidentified compounds (**Scheme 3.21**).

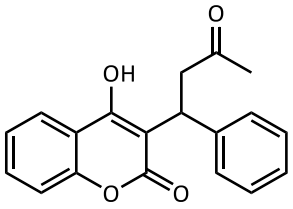


Scheme 3.21. Attempted Suzuki-Miyaura coupling in the presence of other leaving groups.

Interestingly, the reaction of substrate **110** gave the 3-phenyl-4-tosyloxy-2-pyrone **139** as the major product, with both the 3-chloro-4-phenyl-2-pyrone and the 3,4-diarylated product also observed. This result may warrant further development. Compound **139** could not be isolated, but a molecular ion corresponding to its molecular weight was observed in the nominal mass spectrum, and the ^{1}H NMR spectrum of the crude reaction mixture provided evidence for its formation.

3.3.5. Access to 3-aryl-4-hydroxy-2-coumarins

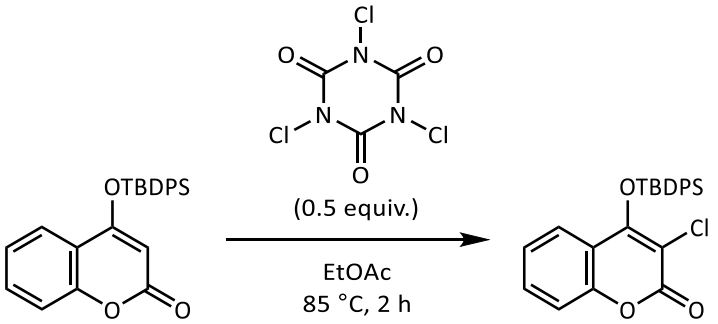
In addition to the important biological activity of 4-alkoxy-2-coumarins and related heterocycles,[31] many important coumarins contain a 4-hydroxy-2-coumarin motif, *e.g.* the anti-coagulant warfarin **140** (**Figure 3.2**).



140

Figure 3.2. Warfarin.

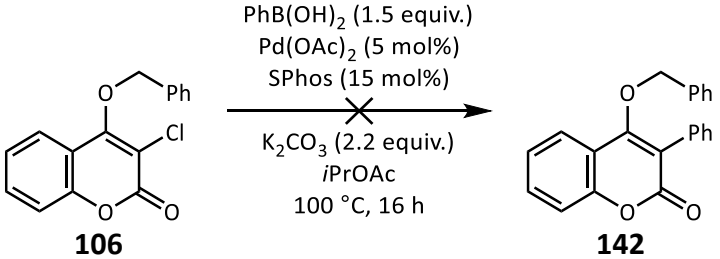
We sought to gain access to 3-aryl-4-hydroxy coumarins *via* hydroxy protection, chlorination, Suzuki-Miyaura coupling and deprotection. However, several common hydroxyl protecting groups, when present on our substrates, either completely inhibited the desired chlorination, or the subsequent Suzuki-Miyaura coupling. For example, a silyl ether (TBDPS) protecting group present in compound **100** did not tolerate the chlorination conditions, and only a 12% yield of the desired product was isolated, which was not synthetically useful (**Scheme 3.22**).



100 **141**, 12%

Scheme 3.22. Attempt to chlorinate 2-coumarin protected with silyl ether.

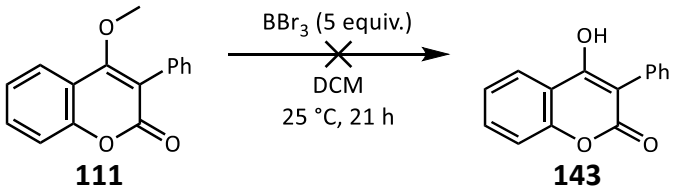
Furthermore, a benzyl ether protecting group did not allow the Suzuki-Miyaura reaction to progress. Only starting material **106** was identified in the ^{1}H NMR spectrum of the crude reaction mixture (**Scheme 3.23**).



106 **142**

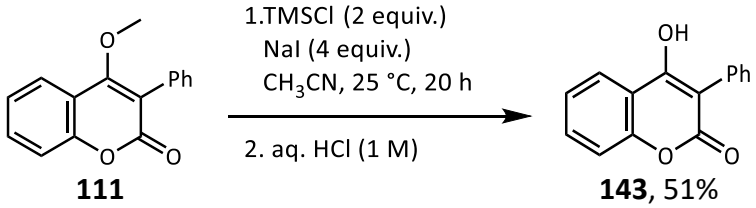
Scheme 3.23. Attempted Suzuki-Miyaura cross-coupling of benzylated 2-coumarin.

Attempts to cleave the methyl ether of compound **111** with BBr_3 were unsuccessful. Based on a procedure by Wiegrebe,[44] coumarin **111** was treated with BBr_3 in DCM (**Scheme 3.24**). Some conversion to product **143** was observed, however, all attempts to drive the reaction to completion were unsuccessful. Using $BBr_3.SMe_2$ was also unsuccessful.



Scheme 3.24. Attempt to demethylate **111** with BBr_3.

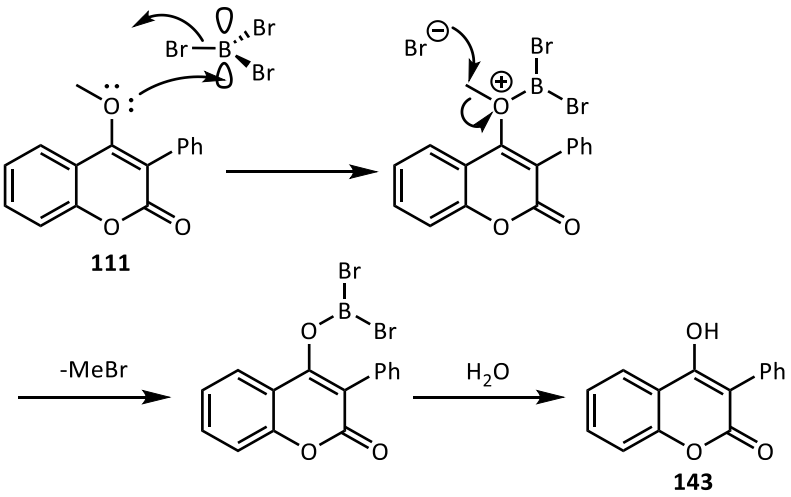
Pleasingly however, a remarkably facile method to cleave the methyl ether of compound **111** at 25 °C was identified (**Scheme 3.25**).



Scheme 3.25. Demethylation of Suzuki-Miyaura product to give 4-hydroxy-3-aryl-2-coumarin.

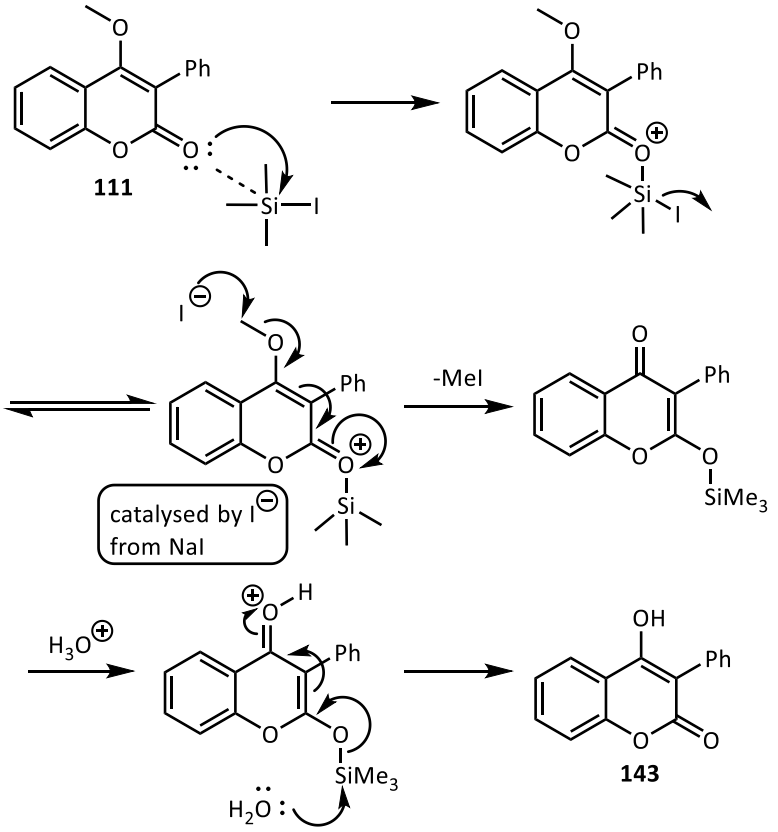
Arylated 2-coumarin **111** was converted to the hydroxyl compound **143** in 51% yield using TMSI[45-46] (formed *in situ* from TMSCl and NaI[47]), followed by an acidic workup. The differing mechanisms of these two sets of conditions provide a rationale for why TMSI deprotection succeeded where BBr_3 deprotection failed.

Scheme 3.26 shows the mechanism for demethylation by BBr_3, which involves the generation of a cation on the oxygen of the methoxy group. This is disfavoured on the 2-coumarin substrate **111** due to resonance localisation of electrons away from the oxygen of the methoxy group and onto the oxygen of the carbonyl. This has a destabilising effect on the positive charge on the methoxy oxygen which is required for the reaction to proceed.



Scheme 3.26. Potential mechanism of BBr_3 demethylation.

On the other hand, demethylation with TMSI is postulated to occur *via* a mechanism catalysed by the iodide ion, which is present in excess due to NaI (**Scheme 3.27**).[47] The protection of the carbonyl as a TMS ether changes the electronics of the molecule, such that there is now an inductive electron-donating effect rather than a resonance electron-withdrawing effect towards the methoxy group. This in turn facilitates the reaction of the methyl group with iodide and MeI is lost. The loss of MeI causes the appearance of an orange colour on the glass of the reaction vessel, which serves as a way to confirm that the reaction is progressing. Aqueous workup with 1M HCl cleaves the TMS ether to give the desired product **143**.



Scheme 3.27. Potential mechanism of TMSI deprotection.

It is noteworthy that previously reported routes to compound such as **143** require cyclisation of the appropriate diester,[48] reactions of diaryliodonium salts,[49] both of which limit diversification, or hazardous diazo compounds.[50]

3.3.6. Conclusions

The Suzuki-Miyaura cross-coupling of 4-alkoxy-3-chloro-2-coumarins in *i*PrOAc, an environmentally benign solvent, has been developed. Chlorination of the 2-coumarin and 2-pyrone framework is achieved through reaction with TCCA, a cheap and environmentally-friendly chlorinating agent. The presented Suzuki-Miyaura reaction conditions are tolerant of a diverse range of aryl and heteroaryl boronic acids. Conditions can be applied to the 2-pyrone, 2-pyridone and 2-quinolone frameworks with equal success. A practically useful demethylation of the Suzuki-Miyaura products allows access to 3-aryl-4-hydroxy-2-coumarins. This deprotection procedure allows the methoxy group, which is easily installed, to act as a protecting group. This proved preferrable to more traditional protecting groups, such as silyl

ethers and benzyl groups, which proved difficult to prepare. Finally, the Suzuki-Miyaura reaction was successfully scaled up to gram quantities.

3.4. Conclusions and Future Work

Two sets of conditions for the Suzuki-Miyaura cross-coupling of 3-chloro-2-pyrones and related heterocycles have been developed. The use of chlorides for cross-coupling is preferable to other halides (iodides and bromides) because chlorides are cheaper and more readily available. A novel method for introducing chlorides into 2-pyrone and 2-coumarin compounds was achieved using TCCA, which is cheaper and more environmentally friendly than NCS. Top pharmaceutical companies are seeking reactions which are executed in non-chlorinated solvents, and the development of Suzuki-Miyaura conditions which can be performed in an environmentally benign solvent such as *i*PrOAc was achieved in this project.

Future work with these conditions could potentially involve their application to the synthesis of biologically active 2-pyrone, 2-coumarin, 2-pyridone or 2-quinolone targets. The availability of a facile deprotection method, *via* demethylation of the Suzuki-Miyaura products, could also prove useful in this regard.

3.5. References

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Chapter 4: Mechanistic insights into the direct arylation of 2-coumarins and related heterocycles

It is precisely facts that do not exist, only interpretations.

Friedrich Nietzsche

4.1. Introduction

In parallel to the synthetic aspects of this project, mechanistic investigations were also performed to develop our understanding of the mechanisms through which 2-coumarins and related heterocycles undergo C–H activation and direct arylation reactions. Insights into the mechanisms of C−H activation reactions are vital to allow extrapolation to untested systems and to inform future development and optimisation of reaction conditions.

For **Section 4.3** and **Section 4.4** of this chapter, the synthetic studies (*i.e.* optimisation of conditions, demonstration of substrate scope, *etc.*) were performed by other members of the McGlacken group, while the mechanistic aspects were studied by the Candidate.

It was necessary to develop a range of protocols to introduce deuterium into the target substrates as part of this work. The experiments which were performed as part of these mechanistic investigations are described. The results are presented and their interpretations are discussed.

A brief introduction to some of the key concepts, such as kinetic isotope effects and deuterium exchange experiments, will be given prior to the discussion of results.

4.1.1. Kinetic isotope effects

In the study of C–H activation reactions, one of the most important experiments utilised are kinetic isotope effect studies.[1-2]

Certain isotopes may differ in their chemical reactivity, because some chemical properties depend on atomic mass. However, this difference is particularly significant for hydrogen because moving from ^{1}H to ^{2}H (deuterium, D) is, in effect, a doubling of mass. The difference is not as significant, for example, between ^{12}C and ^{13}C in chemical reactions, because ^{13}C is only 8% heavier than ^{12}C. In the context of this work, a kinetic isotope effect (KIE) is the change in the rate of reaction observed when a hydrogen (^{1}H) atom is replaced by a deuterium (D) atom in the same reaction,

and can be defined as shown in **Equation 4.1**, where k_H is the rate of reaction with a ^1H atom in the molecule and k_D is the rate with a D atom in the molecule.[2]

$$\mathrm{KIE} = \frac{k_\mathrm{H}}{k_\mathrm{D}}$$

Equation 4.1. Kinetic isotope effect.

Energy is required to raise the vibrational state of the bond to the point where it dissociates. The relationship between energy (*E*) and frequency (*v*) is given by Planck's Law, $E=hv$, where *h* is Planck's constant. The frequency of a stretching vibration is modelled by Hooke's Law for the stretching of a spring with a mass attached at both ends. **Equation 4.2** gives the vibrational frequency of a spring with two masses (m_1 and m_2) at the ends. This equation gives the frequency, *v*, for a harmonic oscillator. The force constant (*k*) for the spring reflects the strength of the bond.

$$\nu = \frac{1}{2\pi}\sqrt{\frac{k}{m_\mathrm{r}}} \text{ where } m_\mathrm{r} = \frac{m_1 m_2}{m_1 + m_2}$$

Equation 4.2. Stretching frequency of a bond.

The frequency, *v*, is directly proportional to the square root of the force constant for the bond, and inversely proportional to the square root of the reduced mass. The reduced mass for a bond between a relatively heavy atom such as C, N or O with a light atom such as H is significantly affected when the H atom is changed to D. The minimum vibrational frequency that a bond can have is called the zero point energy (ZPE). As shown in **Equation 4.2**, the vibrational frequency, and thus the ZPE, depends on the mass (m_1 and m_2) of the atoms attached to the bond. The stretching frequency of a bond with deuterium is reduced due to the heavier mass, and hence the ZPE for the bond is lower also. Since the ZPE for a C–D bond is less than the ZPE for a C–H bond, the C–D bond requires more energy to be broken, *i.e.* C–D bonds are marginally stronger than C–H bonds. KIEs arise because reactions in which C–H bonds break proceed faster than reactions where C–D bonds break, provided that the bond to H (or D) is involved in the rate-determining step (RDS) of the reaction.

If k_H=k_D (*i.e.* k_H/k_D is 1), one could conclude that the bond where the isotopic substitution occurred is not changing during the RDS. However, it may also just be that the isotope effect is too small to be measured accurately. When the ratio of k_H/k_D is different from 1, more reliable conclusions can be drawn. A normal isotope effect is when k_H/k_D is greater than 1. When k_H/k_D is less than 1, it is called an inverse isotope effect. A primary isotope effects means that the isotope effect can be attributed to a bond-breaking event at the substituted bond. When the effect arises from isotopic substitution remote from the bonds undergoing reaction, it is referred to as a secondary isotope effect.[1] Primary isotope effects are of greater magnitude than secondary isotope effects. In essence, the observation of a KIE >1 indicates that C–H/C–D bond cleavage is involved in the RDS of the reaction.

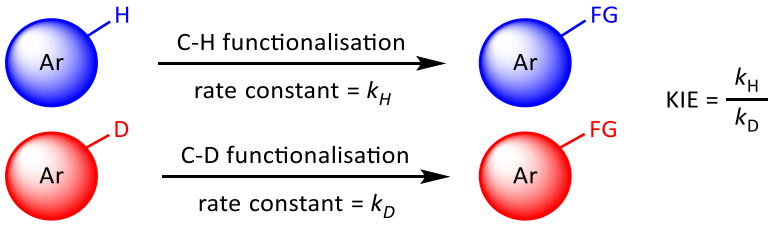
The IUPAC Gold Book recommends that the expressions rate-controlling, rate-limiting and rate-determining be regarded as synonymous, and defines *"the RDS in a reaction occurring by a composite reaction sequence is an elementary reaction the rate constant for which exerts a strong effect – stronger than that of any other rate constant – on the overall rate".*[3] Another important definition to consider is the product-determining step: *"the step of a stepwise reaction in which the product distribution is determined. The product-determining step may be identical to, or occur later than, the rate-controlling step on the reaction coordinate".*[3] It is an irreversible step that controls which of two (or more) possible products are formed in a reaction with multiple competing pathways. Although the product-determining step can also be the RDS, the product-determining step does not need to be the RDS.[4]

Catalytic reaction pathways are often distinct from the corresponding uncatalysed reaction pathways for the same transformation, involving multiple steps and the formation of catalytic intermediates which lower the activation energy of the reaction. Under steady-state conditions, all steps of a catalytic reaction proceed at the same rate by adjustment of the concentrations of the intermediates to offset the differences in the rate constants for each step. Technically, catalytic reactions do not have a "rate-determining step"; rather, the catalytic turnover frequency is controlled by the step with the lowest effective rate constant. This step is called the "turnover-

limiting step".[5] For this chapter, the term "rate-determining step" will be used synonymously with "turnover-limiting step".

There are several types of experiments when can be used to determine a KIE, and each of them can provide different information about the reaction mechanism. The interpretation of KIEs is discussed in an excellent essay by Hartwig,[4] so only a brief summary will be outlined here. The choice of KIE measurement technique and the interpretation of KIE data must be done carefully to avoid conclusions which are unsupported by the available data.

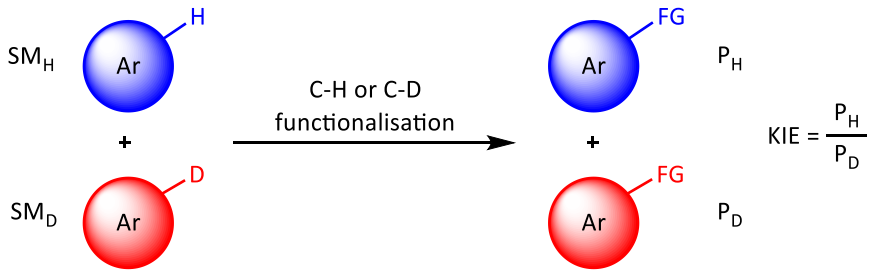
In the first type of KIE experiment, using aryl C–H and C–D bonds as representative examples, two separate rate constants are measured (by NMR spectroscopy, GC, IR spectroscopy, etc.) for two reactions that are conducted in separate flasks, one with a substrate containing a C–H bond and one with a substrate containing an analogous C–D bond. The relative ratio of these independently determined reaction rate constants then gives the reported KIE value (**Scheme 4.1**). The accuracy of the KIE determined by this experiment is limited to the accuracy with which the individual rate constants can be measured. Measurement of the rate constant for a catalytic reaction can be hampered by the presence of induction periods and catalyst decomposition. However, this method of KIE measurement is generally the only one that provides conclusive information on whether the C–H bond cleavage occurs during the turnover-limiting step of a catalytic reaction.



Scheme 4.1. KIE determined from two parallel reactions.

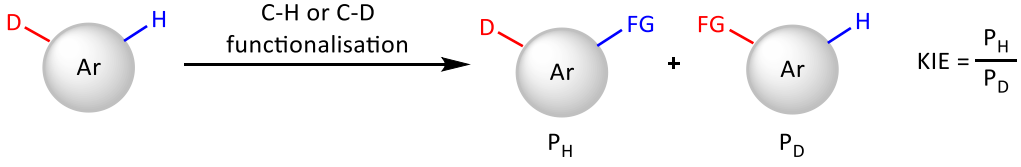
The second type of experiment involves an intermolecular competition between two different substrates in the same reaction flask. Rather than being determined by comparing two reaction rate constants (*i.e.* k_H/k_D) measured separately, the KIE is calculated from the relative amount of products formed by the functionalisation of a

C–H *versus* a C–D bond (*i.e.* P_H/P_D) (**Scheme 4.2**). This method requires just one measurement because both substrates are present in the same flask. This also ensures that the C–H and C–D bond functionalisations both occur under exactly the same conditions, without inadvertent variation. The ratio of reactants and products can be measured with much greater precision than individual rate constants. However, this experiment does not provide the same information on whether C–H bond cleavage occurs during the RDS of a reaction that the first type of experiment does. The absence of an isotope effect would show that C–H bond cleavage does not occur during the RDS, but the observation of a primary isotope effect does not provide evidence that C–H bond cleavage occurs during the RDS, only the experiment shown in **Scheme 4.1** can show that.



Scheme 4.2. KIE determined from an intermolecular competition.

The third type of experiment is conceptually similar to the second but involves an intramolecular competition between functionalisation of a C–H bond and a C–D bond in a single substrate. As is the case in **Scheme 4.2**, the KIE is calculated from the relative amount of products formed from the functionalisation of a C–H *versus* a C–D bond (P_H/P_D).



Scheme 4.3. KIE determined from an intramolecular competition.

The lack of a KIE from this experiment rules out the potential that C–H bond cleavage occurs during the RDS. Therefore, this experiment can provide a simple means to show that C–H bond cleavage is not rate-determining, but the observation of a KIE

from this experiment does not indicate that C–H bond cleavage must occur during the RDS of a reaction. For example, a false positive KIE could be observed if the RDS of a reaction does not involve the substrate that ultimately undergoes C–H bond cleavage.

The competition experiments shown in **Scheme 4.2** and **Scheme 4.3** measure a difference in product distribution that results from a difference in the rate of an irreversible C–H bond-cleavage step, and so these experiments could give rise to a product ratio reflecting a positive KIE, even though the C–H bond cleavage does not occur during the RDS of the overall process. In other words, a positive KIE determined by competition experiments could indicate that the C–H bond cleavage occurs in a step that is product-determining, but not rate-determining.

4.1.2. Hydrogen-deuterium exchange

Hydrogen-deuterium exchange (H–D exchange) is a chemical reaction in which a covalently bonded hydrogen atom is replaced by a deuterium atom, or *vice versa.* This can be applied most easily to exchangeable protons and deuterons. Exchange between XH (where X = O, N or S) protons is extremely fast, and in a deuterated solvent such as D_2O, these exchangeable protons are easily replaced by D. The use of acid, base or metal catalysts, coupled with conditions of increased temperature and pressure, can facilitate the exchange of non-exchangeable hydrogen atoms, provided that the substrate is robust to the conditions applied.

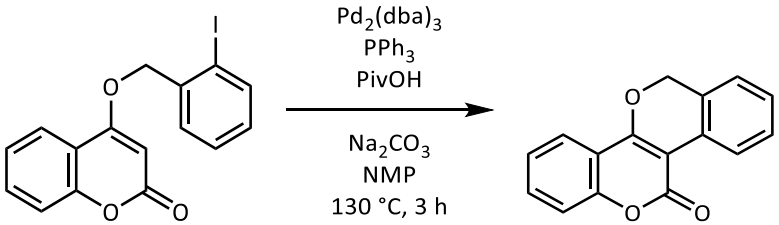
For the study of reaction mechanisms, H–D exchange can be used to identify the source of protons and the reversibility of proton abstraction. For example, if a deuterated analogue of the reaction solvent is used with non-deuterated starting materials, and deuterium is subsequently identified in the starting material and/or product, it may be said that the solvent was the source of the deuterium. Similarly, if a D-labelled starting material is used and the amount of deuterium incorporation is found to be decreased after subjecting it to the reaction conditions, it is inferred that the abstraction of the proton/deuteron at that position is reversible in the reaction. However, this does not necessarily mean that the productive mechanism involves this reversible step, *i.e.* the reversible step could occur as a non-productive, off-cycle

pathway. The inverse experiment is also possible, where a non-deuterated starting material is used and the amount of deuterium incorporation is found to be increased after a period of time. A deuterium source is required for this type of experiment.

Deuterium can be observed by NMR spectroscopy. It is an isotope with a spin = 1, unlike ^{1}H which has a spin = ½. Coupling of deuterium to ^{13}C forms 1:1:1 triplets with a coupling constant of 20-25 Hz, which is a useful way to confirm the presence of deuterium in an isolated compound. ^{2}H NMR has a chemical shift range similar to proton NMR, but peaks show poor resolution. ^{2}H NMR may be used to observe the effectiveness of deuterium incorporation, or deuteration, because a deuterated compound will show a peak in a ^{2}H NMR spectrum but not in a ^{1}H NMR spectrum. For experimental ease, the absence of a previously observed signal by ^{1}H NMR spectroscopy is often used as evidence of deuterium incorporation, and this is the case for all experiments described in this chapter. The extent of deuterium incorporation can also be quantified in this manner. Take, for example, the case of a signal in the ^{1}H NMR spectrum that integrates to 1.00 H (relative to other known non-deuterated peaks in the spectrum) in an unlabelled substrate; if the same signal integrates to 0.01 H in a D-labelled substrate, the labelled substrate is said to have 99% deuterium incorporation at that position. The presence of deuterium can also be observed by MS, as D is 1 amu heavier than ^{1}H.

4.2. Direct arylation *via* single C–H activation at C–3

The first mechanism which will be investigated in this chapter is the direct arylation of 4-benzyloxy-2-coumarin **20** to give the cyclised 2-coumarin **38** (**Scheme 4.4**). The development of these reaction conditions was discussed in **Section 2.2**.



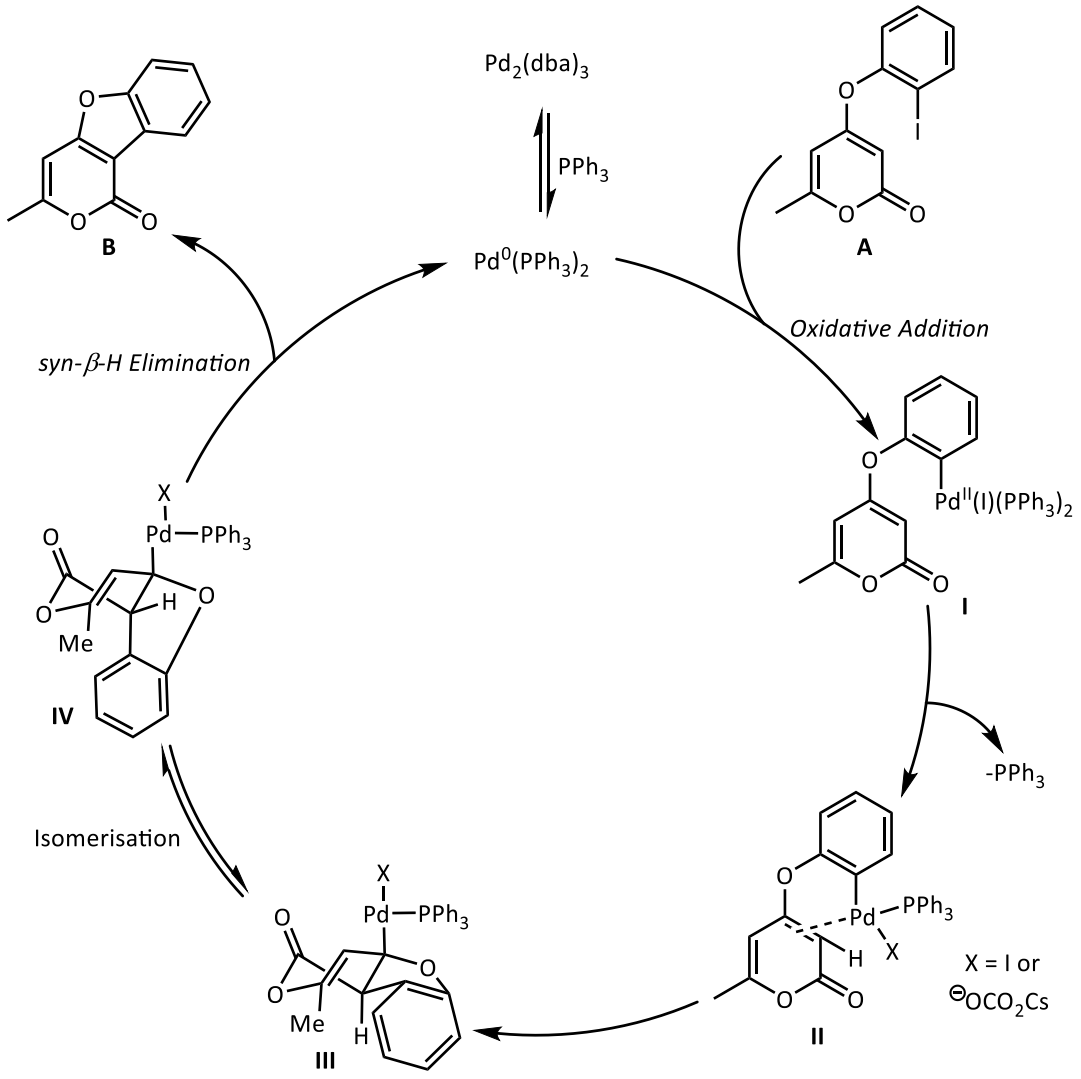
20 **38**, 61%

Scheme 4.4. Direct arylation of 4-benzyloxy-2-coumarin **20**.

Firstly, the understanding of the C–H activation of 2-pyrones and related heterocycles at the time of this work will be outlined.

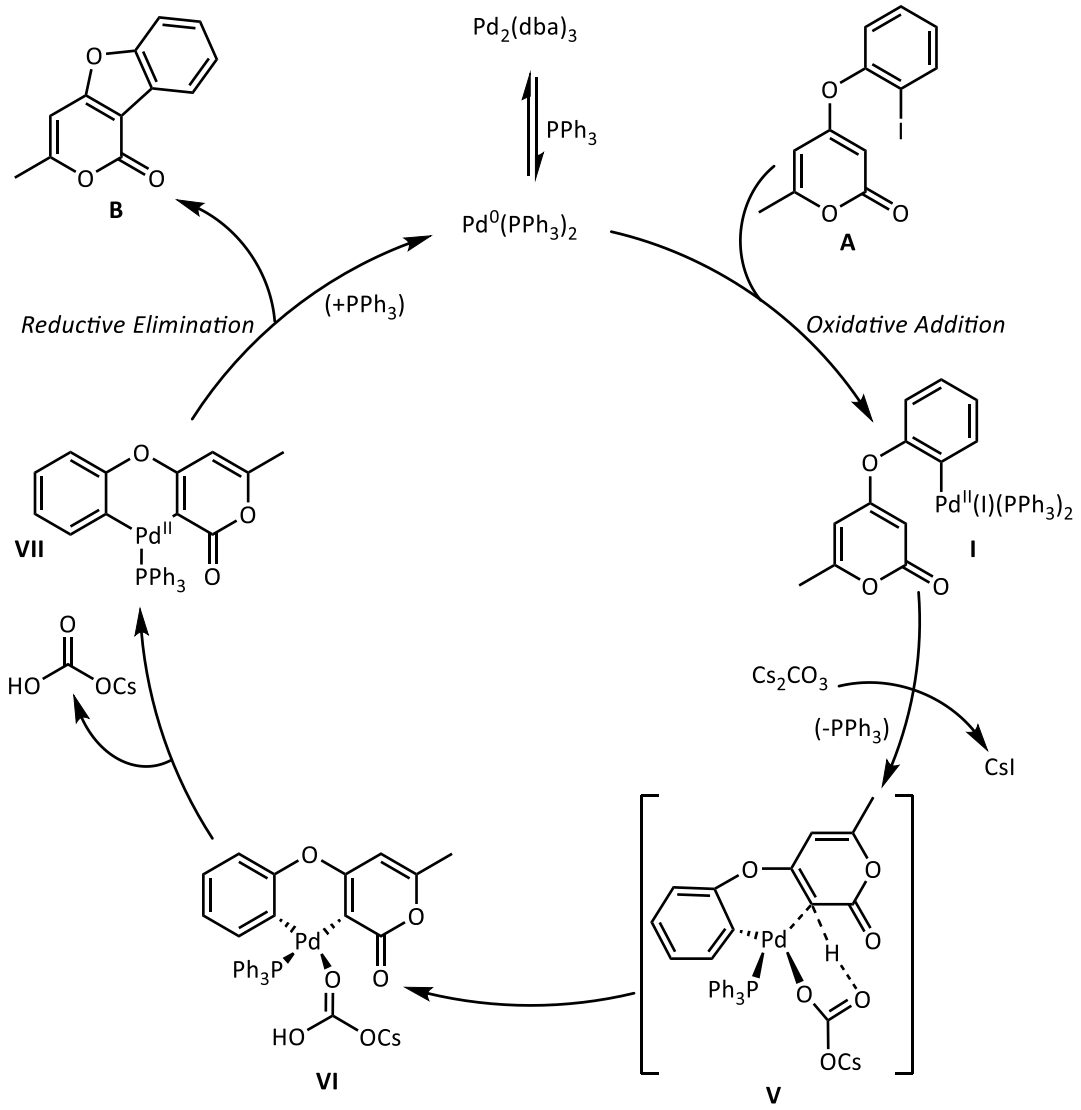
In a report by Fairlamb on direct arylation of 2-pyrone, a number of informative mechanistic experiments were performed.[6] In this report, a mechanism involving neutral palladium intermediates was proposed and two possible mechanistic pathways were entertained: a Concerted Metallation-Deprotonation (CMD)/Ambiphilic Metal-Ligand Assistance (AMLA)[7] mechanism and a Heck-type mechanism.[2] Initially, both mechanisms were considered for the direct arylation of 4-benzyloxy-2-coumarin **20**.

Fairlamb proposed that if a "neutral pathway"[8] Heck-like mechanism was operative then the mechanism could proceed as outlined in **Scheme 4.5**. However, there was an apparent problem in the β-hydride elimination step (**III** to **B**). Since there are no neighbouring *syn*-β-hydrogens, the *anti*-stereochemical relationship of the "Pd(II)(X)PPh_3" group and the C–3 proton is a problem for the β-hydride elimination (**III** to **B**). However, it is possible that isomerisation from **III** to **IV** *via* a π-allyl species allows *syn*-elimination to ultimately occur (**IV** to **B**).



Scheme 4.5. Heck-like mechanism for 2-pyrone arylation proposed by Fairlamb.[6]

The second mechanism proposed involved CMD and is outlined in **Scheme 4.6**.[6] Following the oxidative addition of the Pd(0) species into the C–I bond, the resulting Pd(II) complex **I** was anticipated to undergo ligand exchange whereby one of the phosphine ligands was displaced by a carbonate base, forming intermediate **V**. While it is possible that Cs_2CO_3 deprotonates the C–3 proton of **A** intermolecularly, Fairlamb proposed an iodide/carbonate metathesis to **V** followed by an intramolecular base-assisted CMD process to give intermediate **VII**. Reductive elimination serves to restore the catalyst and expel the arylated product **B**.



Scheme 4.6. Possible CMD mechanism for 2-pyrone arylation.[6]

This is, of course, not an exhaustive outline of the potential mechanisms at play.[6] An S_EAr mechanism could also be possible.[9-10]

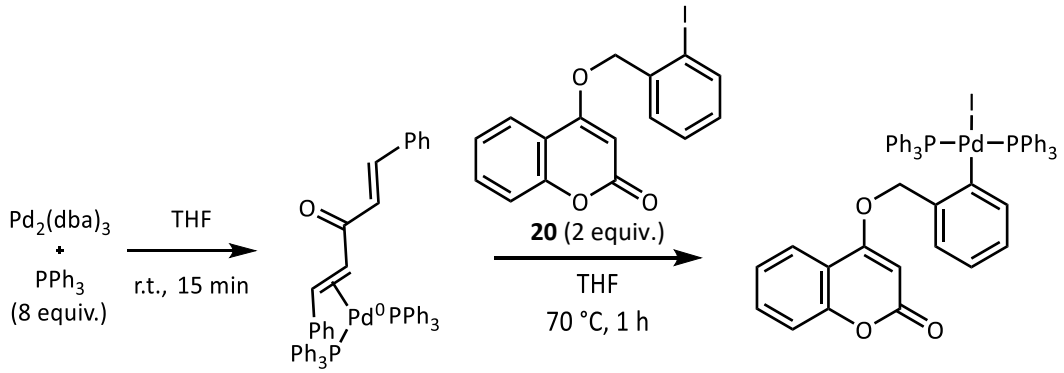
Pivalic acid (PivOH) has been demonstrated to be a promoter of the CMD reaction pathway for C–H activation by Echavarren[11-12] and Fagnou.[13] The pivalate anion is believed to act as a catalytic proton shuttle from the aryl to the stoichiometric carbonate base. As discussed in **Section 2.2.2**, without this additive, very little conversion of starting material to product was obtained.[7] The optimal quantity of PivOH for most published procedures is 30 mol%.[14] Much debate surrounds the existence and engagement of a CMD mechanism in direct arylation reactions. One key paper on the analysis of this mechanism from the Fagnou group in 2008[15] has

been cited over 470 times. Fagnou's report demonstrated that the CMD pathway not only predicts the reactivity and regioselectivity observed with some simple and electron-deficient arenes, but is also applicable to a diverse set of arenes spanning the entire spectrum of known direct arylation coupling partners, including those that have been previously proposed to react *via* S_EAr. Another interesting publication by Fagnou investigated the mechanism of C(sp^3)–H bond cleavage in Pd(0)-catalysed intramolecular arylation of alkanes adjacent to amides and sulphonamides.[14] This report offered fascinating experimental support for the CMD transition state using stoichiometric studies, KIE experiments and DFT calculations. Further information was also provided on an important, additional role of pivalate as a promoter of phosphine dissociation from the Pd(II) intermediate, enabling the CMD transition state.

4.2.1. Investigation of the oxidative addition intermediate

For the investigation into the direct arylation of 4-benzyloxy-2-coumarin **20** to give the cyclised 2-coumarin **38** (**Scheme 4.4**), the first experiments were conducted to deduce if oxidative addition to the aryl halide was the preliminary step in the reaction mechanism. This could be evidence for either a Heck-type or CMD-type mechanism as described in **Section 4.2**. The isolation and characterisation of the oxidative addition product formed during these reactions was investigated. It was previously demonstrated by McGlacken and co-workers that reaction of $Pd_2(dba)_3$ with PPh_3 gave Pd(0)(η^2-dba)(PPh_3)$_2$ (**144**), and that 8 equivalents of PPh_3 was necessary to displace the dba ligand and to stabilise the oxidative addition product.[16]

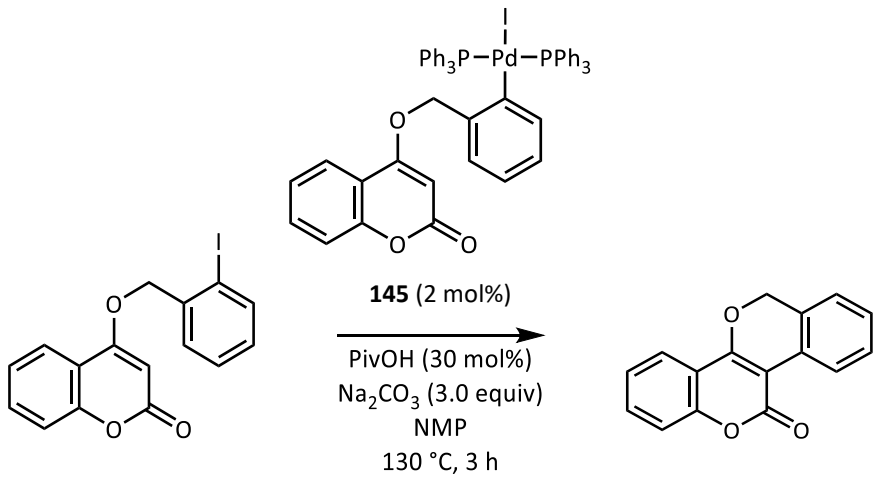
As shown in **Scheme 4.7**, 1 equivalent of $Pd_2(dba)_3$ was reacted with 8 equivalents of PPh_3 in THF at room temperature, followed by the addition of 2 equivalents of coumarin **20**. Oxidative addition product [Pd{(C_7H_6O-2-($C_9H_5O_2$))}I(PPh_3)$_2$] (**145**) was isolated from this reaction as a grey solid in 90% yield. Intermediate **145** was then characterised by NMR spectroscopy. A single peak was observed in the ^{31}P NMR spectrum (22.8 ppm), characteristic of Pd(II) coordination.



144 **145**, 90%

Scheme 4.7. Isolation of oxidative addition intermediate **145**.

The nature of [Pd{(C_7H_6O-2-($C_9H_5O_2$))}I(PPh_3)$_2$] (**145**) as a catalytically relevant intermediate was then established. It was with this aim that 4-((2-iodobenzyl)oxy)-2-coumarin (**20**) was subjected to the optimised reaction conditions, replacing $Pd_2(dba)_3$ (2 mol%) and PPh_3 (4 mol%) with [Pd{(C_7H_6O-2-($C_9H_5O_2$))}I(PPh_3)$_2$] (**145**) (2 mol%). The cyclised product **38** was obtained in 55% yield, comparable to 61% under the standard reaction conditions. This indicates that **145** is likely to be an intermediate in the direct arylation reaction (**Scheme 4.8**).[14]



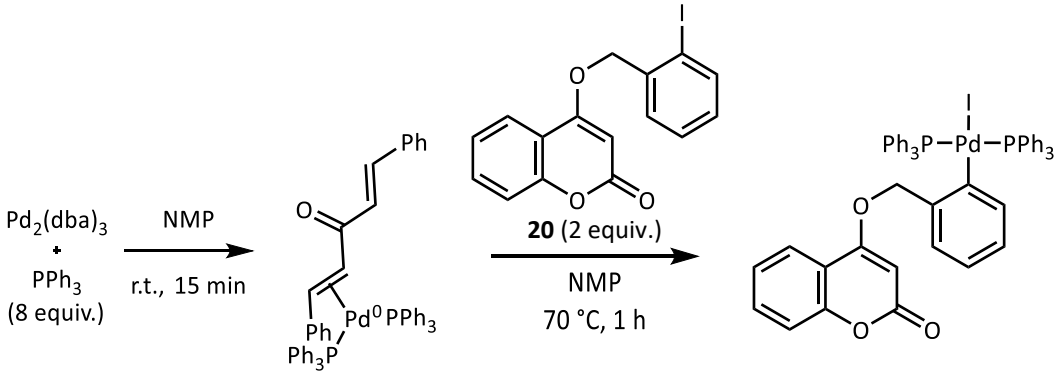
20 **38**, 55%

Scheme 4.8. Cyclisation reaction using oxidative addition intermediate **145** in place of $Pd_2(dba)_3$/PPh_3.

The reaction shown in **Scheme 4.8** was also performed in the absence of PivOH, resulting in a 3% yield of arylation product **38**. This provides further evidence that PivOH is a necessary co-catalyst in this system. It could also be interpreted as

evidence that these arylation reactions proceed *via* CMD, based on the work by the Fagnou group which demonstrates the importance of PivOH as a promoter of phosphine dissociation from the Pd(II) intermediate, enabling the CMD transition state,[14] and as a catalytic proton shuttle[13] in the CMD mechanism. The need for both pivalate and carbonate anions in CMD systems has been rationalised by the requirement for a soluble basic species responsible for deprotonation of the aryl (pivalate) and an insoluble proton sink responsible for the sequestration of H^+ and pivalate regeneration (carbonate).[13-14]

Since intermediate **145** was isolated from a reaction using THF as the solvent, it was important to investigate if this same intermediate could form in the more polar NMP, which is the optimal reaction solvent. Again, 1 equivalent of $Pd_2(dba)_3$ was reacted with 8 equivalents of PPh_3 at room temperature, but this time in NMP, followed by the addition of 2 equivalents of coumarin **20**. [Pd{(C_7H_6O-2-($C_9H_5O_2$))}I(PPh_3)$_2$] (**145**) was identified by ^1H and ^{31}P NMR spectroscopy after the reaction mixture had been stirred at 70 °C for 1 h (**Scheme 4.9**).



Scheme 4.9. Identification of oxidative addition intermediate **145** in NMP.

Na_2CO_3 (10 equiv.) and PivOH (3 equiv.) were then added to the reaction mixture and the reaction stirred at 130 °C for a further 3 h, after which the cyclised product **38** was determined to have formed in 47% yield; this is comparable to results (61% yield) after standard catalytic conditions are applied. The stoichiometric amounts of base and PivOH were found to be necessary by Fagnou in a similar experiment, in order to mimic the ratios of pivalate and carbonate to palladium.[14]

Taken together, these experiments demonstrate that oxidative addition of a Pd(0) catalytic species into the C–I bond of the 4-benzyloxy group to give intermediate **145** is a step in the mechanism of the direct arylation of substrate **20** to give product **38**.

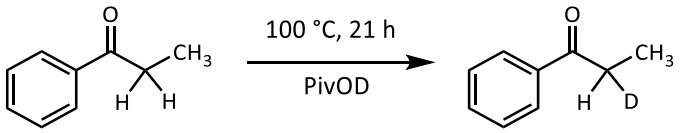
4.2.2. Investigation of the C–H activation at C–3

The C–H activation event at the C–3 position of the 2-coumarin substrate **20** was the next mechanistic step to be investigated. Deuterium exchange and KIE experiments were performed in the investigation of this step.

C–H activation as the first step

The possibility that the initial step in the mechanism could involve a reversible C–H activation was examined. This is well-known for rhodium-based catalysts,[17] but in cases involving palladium, usually a Pd(II)/Pd(IV) mechanism is invoked. Given the apparent acidity of the C–3–H bond,[6] the potential for an initial reversible C–H bond activation was considered. This was assessed using three tests with deuterated pivalic acid (PivOD). PivOD was prepared by heating PivOH at 55 °C in D_2O overnight. As outlined in **Section 4.1.2**, exchange between XH (where X = O, N or S) protons is extremely fast, and in a deuterated solvent such as D_2O, these exchangeable protons are immediately replaced by D.

To confirm the presence of deuterium in PivOD, an exchange experiment was performed with propiophenone (**146**). The α-protons of propiophenone are exchangeable due to keto-enol tautomerism. After heating for 21 h, the CH_2 quartet at 3.00 ppm appeared as multiplet integrating as 1H relative to the aromatic protons, indicating that deuterium had been incorporated at the α-position to give compound **147** (**Figure 4.1**).



146 **147**

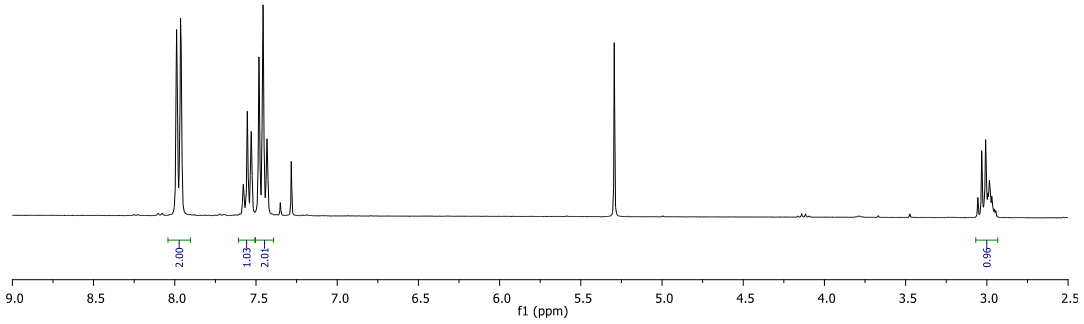


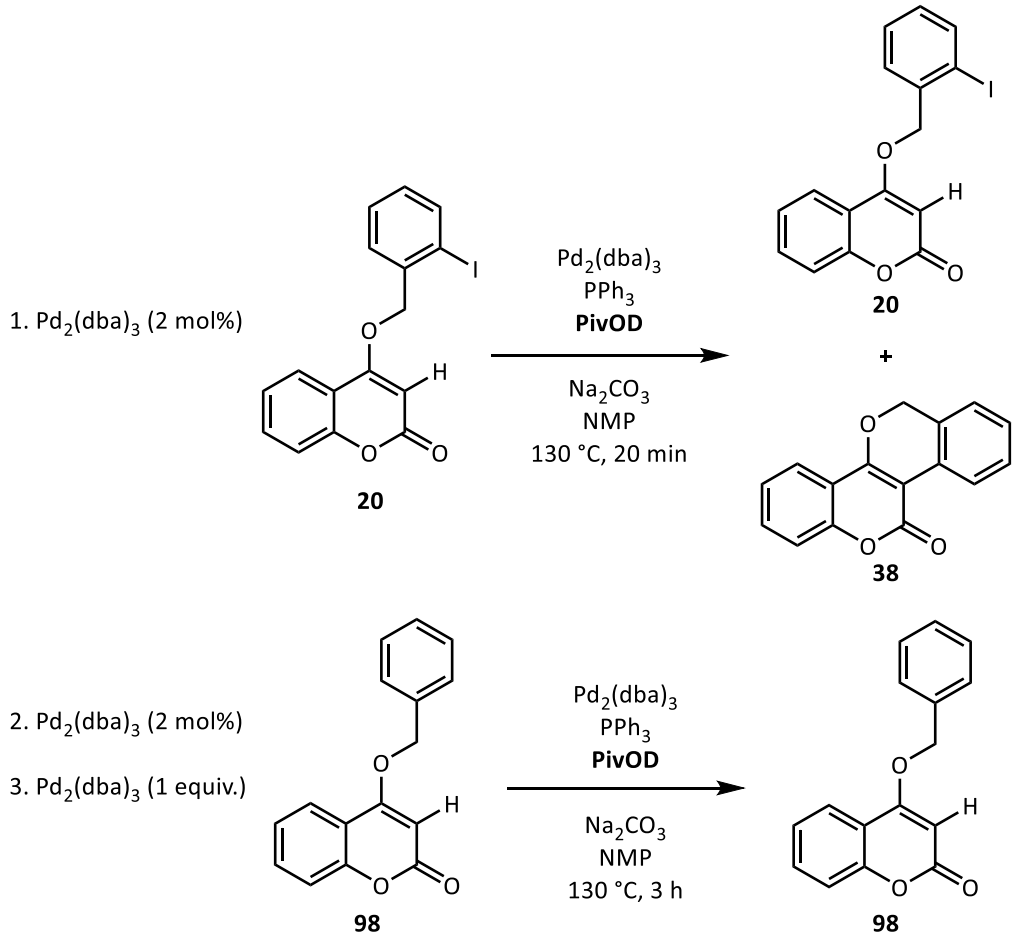
Figure 4.1. Confirmation of deuterium incorporation in PivOD.

To investigate the possibility of reversible C–H activation, the H–D exchange experiments (**Scheme 4.10**) consisted of:

1. Exposing the coumarin starting material **20** to the optimised reaction conditions in the presence of PivOD and halting the reaction before completion.

2. Using an unhalogenated variant **98** under the standard conditions with PivOD.

3. Using an unhalogenated variant **98** with PivOD but with a stoichiometric amount of the palladium and phosphine sources.



Scheme 4.10. Investigatation of reversible C–H activation.

All three tests failed to give any deuterium incorporation. For substrate **20**, deuterium incorporation would have shown that reversible pivalate-assisted C–H activation occurred after oxidative addition into the C–I bond. For tests involving the unhalogenated variant **98**, any deuterium incorporation would have shown that reversible pivalate-assisted C–H activation occurred before oxidative addition into the C–I bond. These results allowed the elimination of pivalate-assisted reversible C–H activation as a potential first mechanistic step.

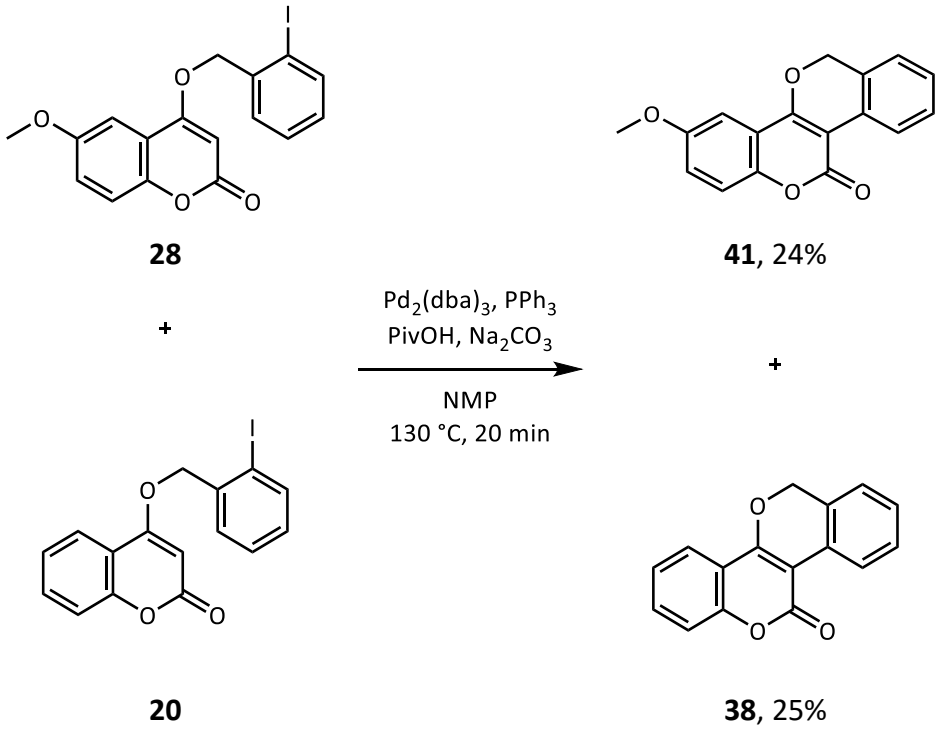
Electronic effects of 2-coumarin ring substitution

As described in **Section 2.2.3**, it was found that good yields of 71-82% were observed for electron-rich 2-coumarins. A slight reduction in yield was noted for electron-poor 2-coumarins. For example, the 6-fluoro **42** and 6-nitro **43** products formed in 43% and 58% yields respectively. Fagnou reported that there is an important C–H bond acidity parameter in regioselectivity and reactivity; results which were incompatible

with S_EAr and radical processes, but correlated well with a proton-transfer pathway.[13] Computational studies revealed the key C–H functionalisation step occurs *via* a CMD process, the accessibility of which depends directly on the acidity of the C–H bond being cleaved.[18]

Thus, the effect of C–H acidity on the direct arylation of 2-coumarins was investigated by conducting competition reactions. Substitution of the 6-position of the 2-coumarin ring was expected to affect the acidity C–3–H bond due to resonance delocalisation of electrons.

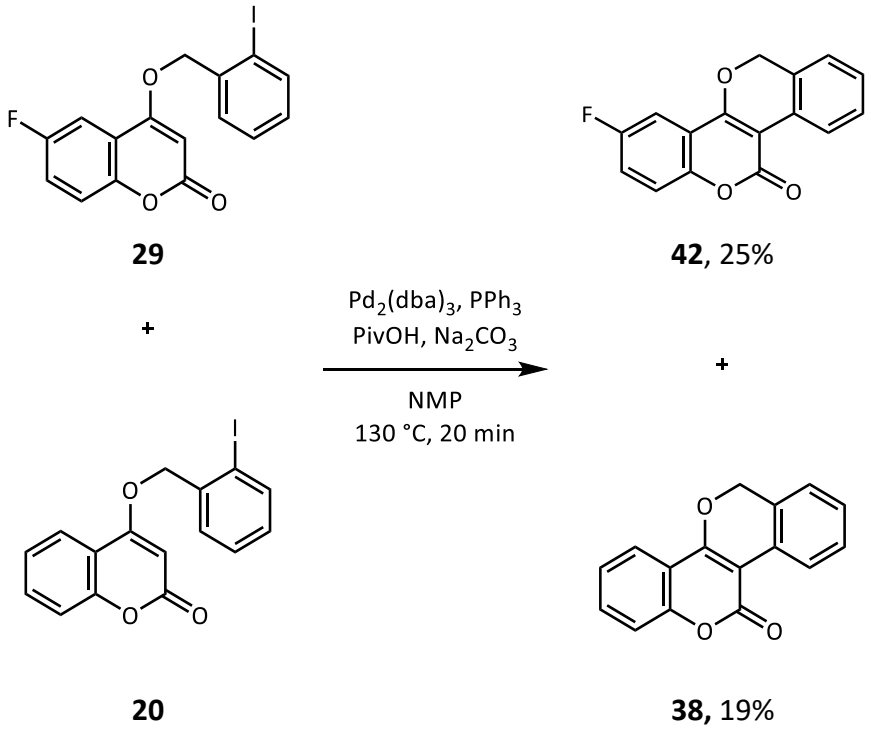
However, in a one-pot competition experiment between the unsubstituted 2-coumarin **20** and the less acidic 6-methoxy 2-coumarin **28** (**Scheme 4.11**), both substrates appeared to react at a similar rate.



Scheme 4.11. Competition experiment between 6-methoxy **28** and 6-hydro **20** 2-coumarins. Yields were determined from the ^{1}H NMR spectrum of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard for quantification.

The reaction time during the substrate scope was 3 h, but for the competition experiments, the reactions were stopped early. Both product **38** and product **41** were present in ~25% yield after 20 min, as determined from the ^{1}H NMR spectrum of the crude reaction mixture.

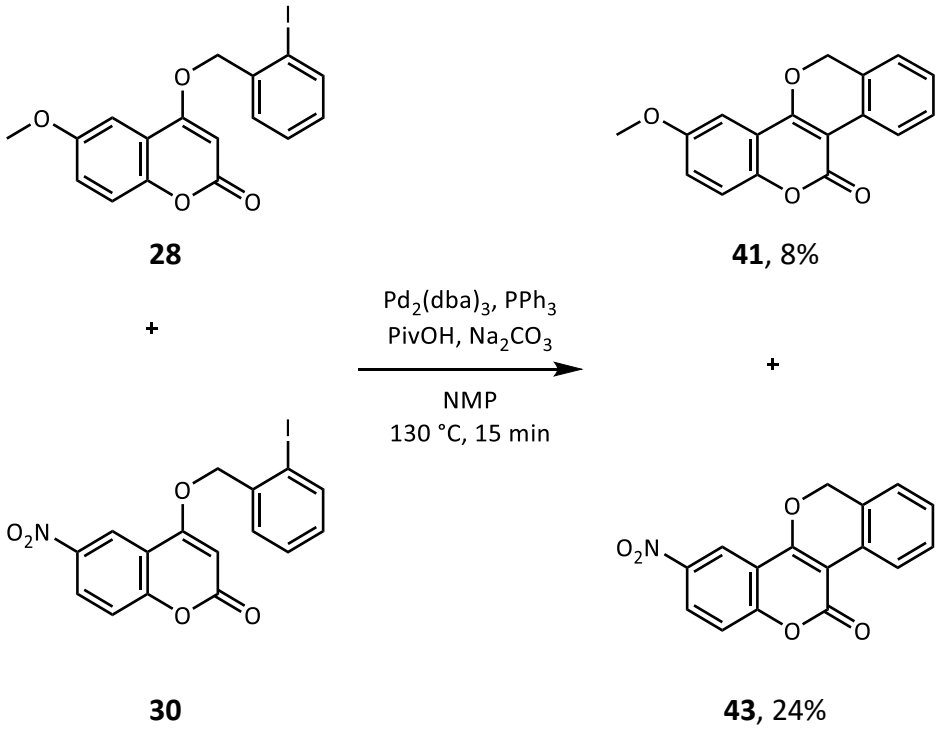
A second one-pot competition experiment between the unsubstituted 2-coumarin **20** and the more acidic 6-fluoro 2-coumarin **29** was then conducted (**Scheme 4.12**).



Scheme 4.12. Competition experiment between 6-fluoro **29** and 6-hydro **20** 2-coumarins. Yields were determined from the ^{1}H NMR spectrum of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard for quantification.

The more acidic substrate **29** reacts at a slightly faster rate and product **42** was present in 25% yield after 20 min, while product **38** was present in 19% yield according to the ^{1}H NMR spectrum of the crude reaction mixture.

Finally the rate of reaction of a 2-coumarin bearing a strongly electron-withdrawing 6-nitro group **30** and the rate of reaction of a 2-coumarin bearing a 6-methoxy group **28** were compared *via* a one-pot competition experiment. Product **43** is formed in 24% yield in just 15 min, while substrate **28**, which presumably has a less acidic C–H bond, gives product **41** in only 8% yield under the same conditions.



28 + **30** → **41**, 8% + **43**, 24%

Scheme 4.13. Competition experiment between 6-methoxy **28** and 6-nitro **30** 2-coumarins. Yields were determined from the ^{1}H NMR spectrum of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard for quantification.

The presence of the electron-withdrawing groups at the 6-position should make the C–3–H bond more acidic. This in turn makes substrates bearing electron-withdrawing groups more reactive towards the CMD pathway for direct arylation, which could explain why greater yields were observed for substrate **30** compared to substrate **28** bearing an electron-donating methoxy group. This is in line with Fagnou's observations regarding the importance of C–H bond acidity in the CMD pathway.[13, 18] However, this is in contradiction with the observed yields for these compounds in the substrate scope (**Scheme 2.19**). In the substrate scope, compound **41** was isolated in 82% yield after the 3 h reaction time, while product **43** was isolated in 58% yield. The same reaction time was applied to every substrate, so it is possible that the products bearing EWGs formed faster than the compounds bearing EDGs, and then degraded over the prolonged reaction time.

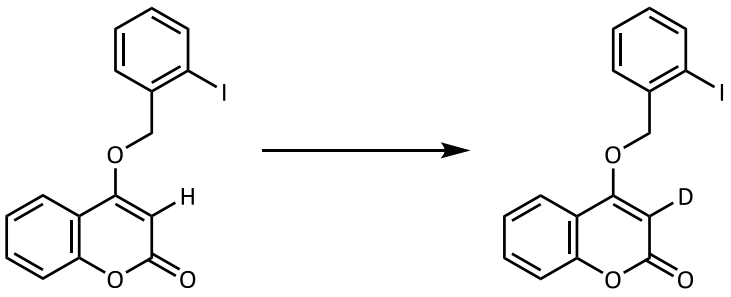
In hindsight, it may have been more useful to locate the substituents at the 7-position as this would have maximised the resonance delocalisation towards the C–3–H bond.

Investigation of the kinetic isotope effect

The theory behind KIEs, as well as common experiments to determine KIEs, is discussed in **Section 4.1.1**. To examine the KIE at the C–3 position, it was necessary to synthesise a deuterated variant of 2-coumarin **20**, which required extensive optimisation.

Initially, it was attempted to access deuterated 2-coumarin **148** *via* H–D exchange of 2-coumarin **20** using D_2O under a range of conditions (**Table 4.1**).

Table 4.1. Initial investigation of deuteration conditions.



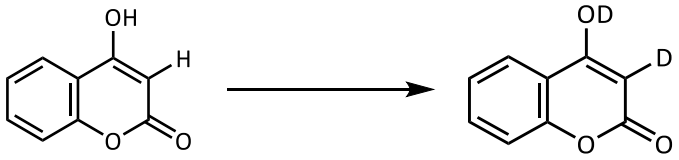
20 **148**

Entry	Reagents	T (°C)	t (h)	C–3 Deuteration (%)
1	D_2O, dried acetone	79	16	0
2	AcOD, D_2O	79	48	0
3	Na_2CO_3, D_2O, acetone-d_6	79	96	degradation

It was found that neutral (**Table 4.1**, **entry 1**) and acidic conditions (**Table 4.1**, **entry 2**) did not facilitate H–D exchange of the C–3 proton of **20**. Basic conditions over an extended time frame degraded the starting material (**Table 4.1**, **entry 3**).

It was then decided to attempt to deuterate the parent 4-hydroxy-2-coumarin (**19**), and benzylate the deuterated compound **149**. To introduce deuterium to 4-hydroxy-2-coumarin (**19**), a variety of conditions were tested (**Table 4.2**).

Table 4.2. Deuteration of 4-hydroxy-2-coumarin (**19**).

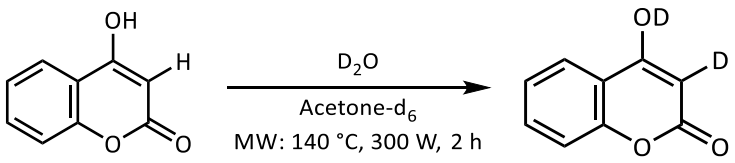


19 **149**

Entry	Reagents	T (°C)	Time	C–3 Deuteration (%)
1	AcOD, D_2O	79	48 h	0
2	K_2CO_3, D_2O, dried THF	79	4 h	6
3	DCl, D_2O	100	96 h	30
4	D_2O, dried acetone	25	1 h	21
5	D_2O, dried acetone	79	18 h	44
6	D_2O, acetone-d_6	79	2 x 48 h	54
7	D_2O, acetone-d_6	79	4 days	79
8	D_2O, acetone-d_6	79	7 days	87

Acidic (**Table 4.2**, **entries 1 & 3**) and basic (**Table 4.2**, **entry 2**) conditions gave poor deuterium incorporation, while neutral conditions required long reaction times for any considerable incorporation to occur (**Table 4.2**, **entries 4-8**). Deuterium incorporation in the isolated product also tended to decrease over time, even if the flask was filled with nitrogen and stored in the freezer. This can be explained by keto-enol tautomerism, making the C–3 proton of **149** highly labile.

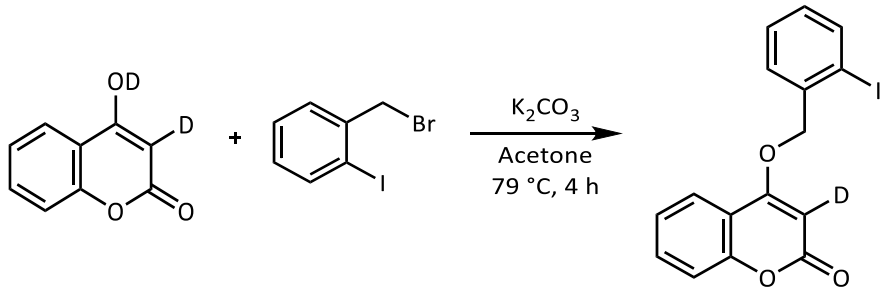
In an attempt to reduce the reaction time, microwave conditions were applied. After 2 h at 140 °C with 300 W of power, 90% deuterium incorporation was achieved (**Scheme 4.14**).



19 **149** (90% D)

Scheme 4.14. Deuteration of 4-hydroxy-2-coumarin (**19**) under microwave conditions.

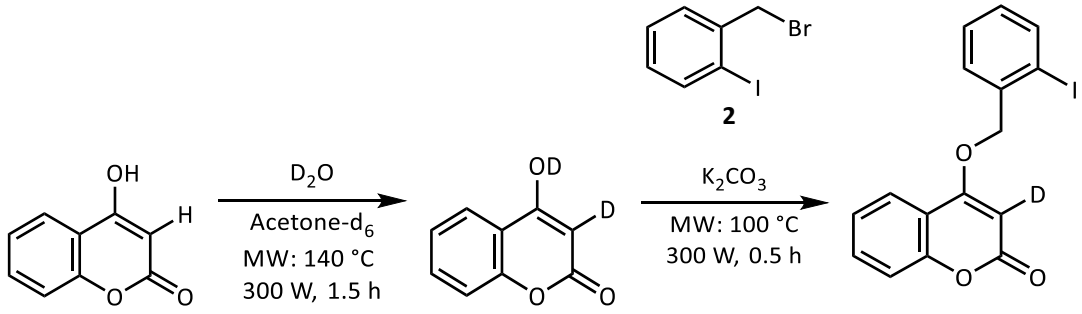
The sample of product **149** with the highest deuterium incorporation was benzylated (**Scheme 4.15**). The level of deuterium incorporation was retained during the benzylation reaction, and the deuterium incorporation did not decrease over time in the benzylated compound **148**.



149 (90% D) **2** **148** (90% D)

Scheme 4.15. Benzylation of deuterated 2-coumarin **149**.

To maximise the deuterium incorporation in the target substrate **148**, a one-pot deuteration/benzylation procedure under microwave conditions was developed (**Scheme 4.16**).



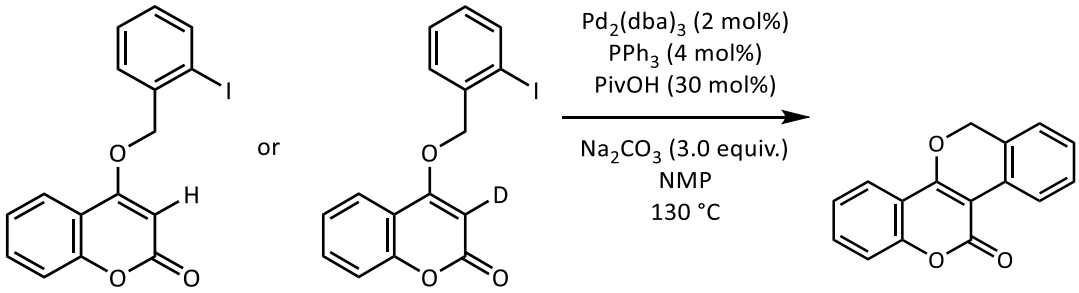
19 **149** **148**, 43% (98% D)

Scheme 4.16. One pot deuteration/benzylation procedure.

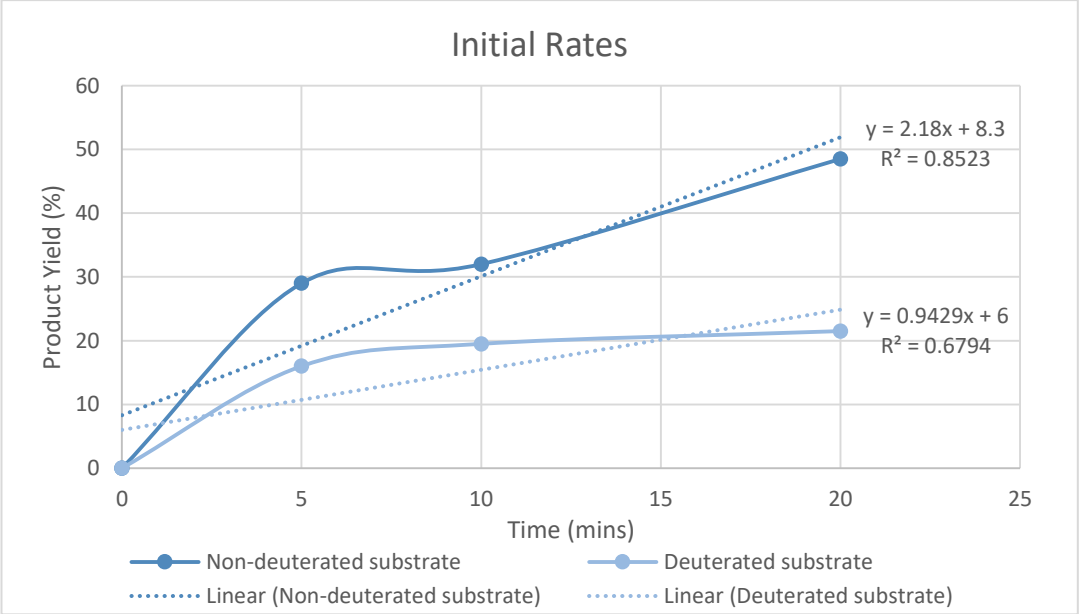
4-Hydroxy-2-coumarin (**19**) was dissolved in a mixture of D_2O and acetone-d_6 and stirred in a microwave reactor at 140 °C for 1.5 h. The microwave vial was removed from the reactor, and 2-iodobenzyl bromide (**2**) and K_2CO_3 were added to the reaction mixture. The vial was placed back in the reactor where the mixture was stirred at 100 °C for 0.5 h. Thus, after a total of 2 h reaction time, the reaction mixture was worked up and columned, to give product **148** with 98% deuterium

incorporation at C–3. A sample of the substrate could be stored at ambient temperature with no loss of deuterium incorporation, for at least one month.

The KIE at C–3 was determined by the initial rates method (**Figure 4.2**).[19] The rate of reaction for the non-deuterated substrate **20** and the deuterated substrate **148** for the formation of product **38** was determined by setting up six pairs of parallel reactions. The pairs of reactions were stopped at the indicated time points, and the yield of each reaction was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard for quantification. The experiment involving 12 reactions was performed in duplicate. The yields of product **38** at each time point were averaged, and the averaged yields were plotted against time to give **Figure 4.2**. This type of experiment allows one to conclude whether the C–H activation is the rate-determining step, as discussed previously.[4]



20 **148** **38**



$$\text{KIE} = \frac{k_{\text{H}}}{k_{\text{D}}} = \frac{\text{m}_1}{\text{m}_2} = \frac{2.18}{0.9429} = 2.3$$

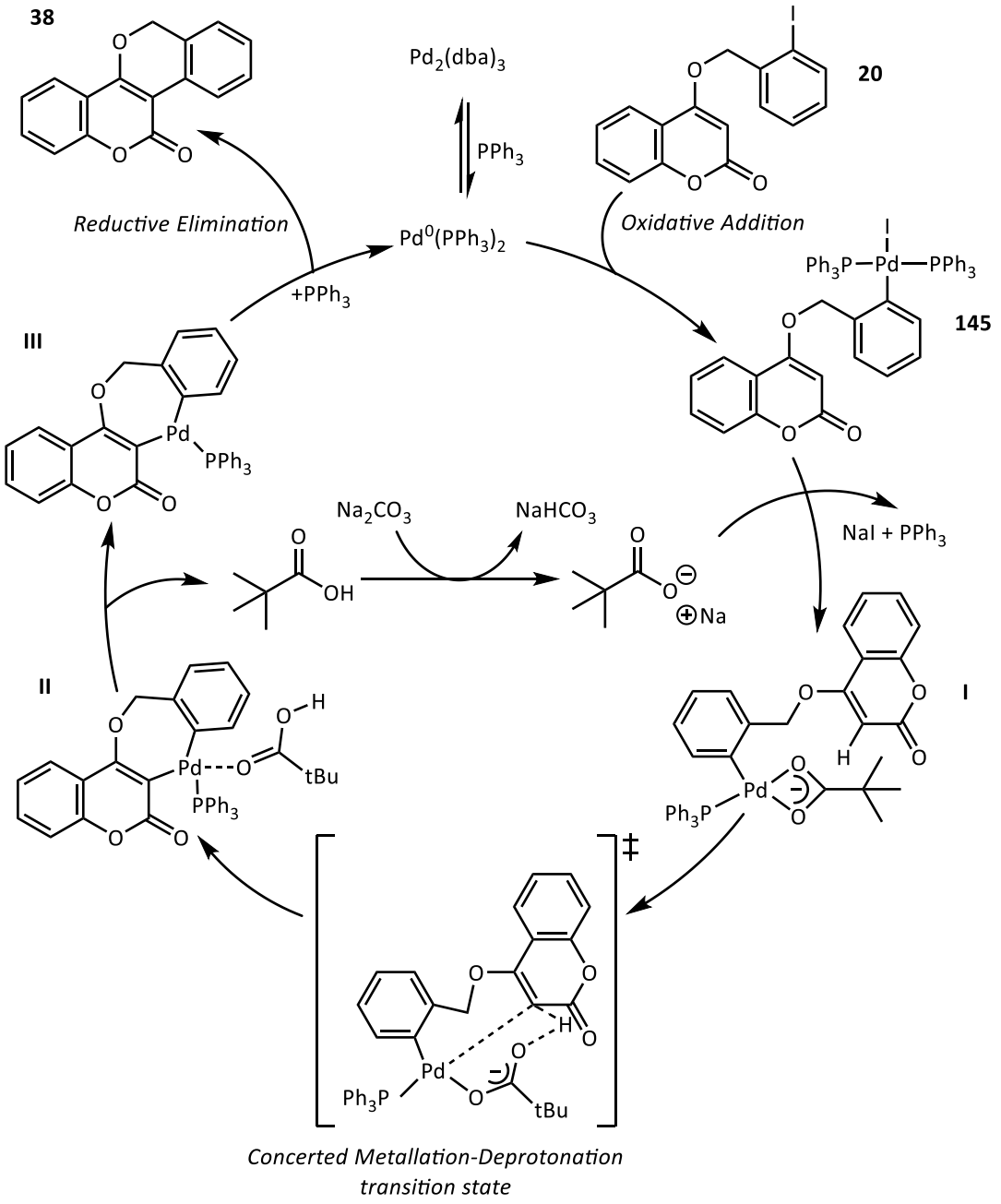
Figure 4.2. Determination of kinetic isotope effect.

Using this method, the KIE was determined to be 2.3. This is a significant positive KIE and therefore it is concluded that C–H activation is the rate-determining step of the mechanism. The observation of a significant positive KIE from this experiment is incompatible with both Heck-type and S_EAr mechanisms.

4.2.3. Conclusions

Based on these results, it is envisioned that a CMD mechanism is at play in this system (**Scheme 4.17**). Following the oxidative addition of the Pd(0) species into the C–I bond, the resulting Pd(II) complex **145** is anticipated to undergo ligand exchange whereby one of the phosphine ligands is displaced by a pivalate base, forming

intermediate **I**. This process has been shown to be promoted by PivOH.[14] While it is possible that Na_2CO_3 deprotonates the C–3 proton of **20** intermolecularly, instead an iodide/pivalate metathesis to **I** followed by an intramolecular base-assisted CMD process to give intermediate **II** is proposed, based on the work by Fagnou,[7, 13] Echavarren[11] and Davies/Macgregor.[20-21] The pivalate anion is believed to act as a catalytic proton shuttle from the aryl to the stoichiometric carbonate base (proton sink).[13] Reductive elimination from **III** serves to restore the catalyst and expel the arylated product **38**.

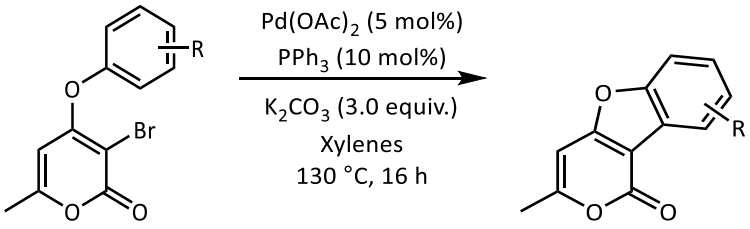


Scheme 4.17. Proposed CMD mechanism for direct arylation of 2-coumarin substrates.

4.3. Direct arylation *via* single C–H activation of an aryl C–H bond

The intramolecular direct arylation of 2-pyrones to form five-membered[6, 22-23] and six-membered[16, 24-26] rings has been well-studied by the McGlacken group and others. In these examples, the coupling was realised between a C–H bond on the 2-pyrone and a C–X bond on the aryl ring. Such coupling reactions presumably proceed *via* well-known oxidative addition of Pd to the aryl halide, followed by C–H activation of the 2-pyrone. The C–3 proton of 2-pyrones has been shown to be acidic,[6] making base-assisted proton abstraction a facile process. However, this approach has its limitations. 2-Pyrones have two potential sites for C–H activation (C–3 *versus* C–5), and thus complete regioselectivity is not guaranteed when the C–X bond is situated on the aryl ring. Also, halogenated phenoxy and benzyloxy coupling partners can be expensive to access, while the corresponding di- and tri-substituted phenols and benzyl alcohols are considerably cheaper. Poor yields when using electron-poor aryl halide coupling partners has proved a limitation of previous studies.[6] All of these issues can be overcome by taking a more challenging approach to the direct arylation reaction: Using a halogenated 2-pyrone and activating the C–H bond of the phenoxy-based coupling partner. Coupling involving an iodide on the 2-coumarin framework is known.[27-28]

Within the McGlacken group, conditions were developed which facilitated the intramolecular direct arylation of 3-bromo-4-phenoxy-2-pyrones (**Scheme 4.18**).[29-30] Yields were moderate to excellent (40-93%), and electron-withdrawing substituents on the phenoxy ring were tolerated.



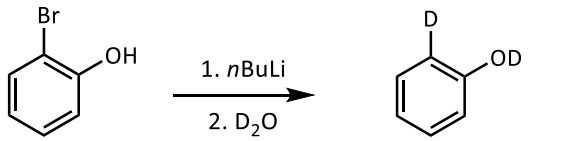
Scheme 4.18. Direct arylation of 3-bromo-4-phenoxy-2-pyrones.

Work on this section of the project involved the synthesis of a deuterated analogue of the 3-bromo-4-phenoxy-2-pyrone substrate, and subsequent determination of the KIE. The experiments, results and interpretations will be discussed.

4.3.1. Investigation of the kinetic isotope effect of the aryl C–H bond

To examine the KIE, it was decided that an intramolecular competition experiment (**Section 4.1.1, Scheme 4.3**) would be performed because it is easy to conduct and gives an accurate result. The absence of a kinetic isotope effect would show that C–H activation is not involved in the rate-determining step.[4] However this type of experiment does not allow the confirmation of C–H activation as the rate-determining step.

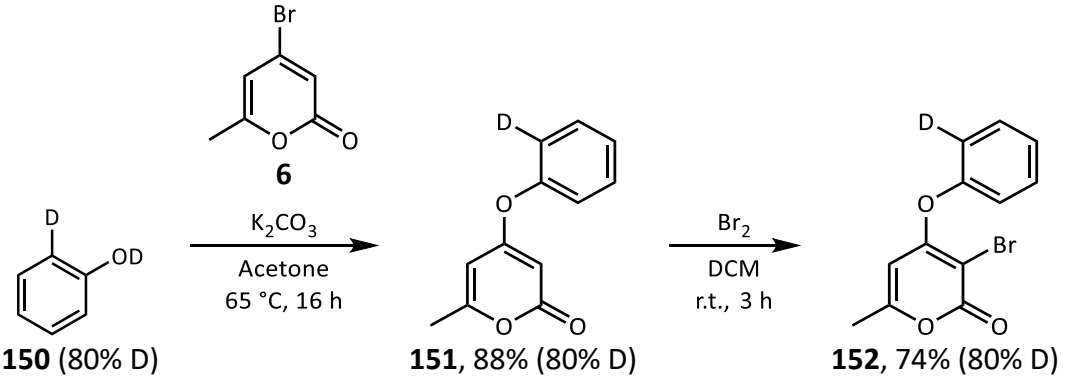
Following the literature procedure,[31] 2-bromophenol was treated with 2 equivalents of *n*BuLi at 0 °C for 3 h to generate a lithiated dianion, which when quenched with D_2O gave 2-deuteriophenol **150** in 62% yield after column chromatography, with 80% incorporation of deuterium at the indicated position (**Scheme 4.19**).



150, 62% (80% D)

Scheme 4.19. Synthesis of 2-deuteriophenol **150**.

2-Deuteriophenol was subsequently reacted with 4-bromo-2-pyrone **6** overnight under basic conditions to give **151** in 88% yield with the retention of deuterium (**Scheme 4.20**). No purification was required. Compound **151** was then brominated with Br_2 and purified by recrystallisation to give the target substrate **152** in 74% yield, again with 80% deuterium at the indicated position.



150 (80% D) **151**, 88% (80% D) **152**, 74% (80% D)

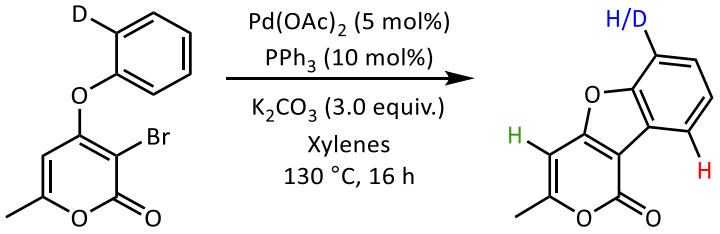
Scheme 4.20. Synthesis of substrate **152** for kinetic isotope effect study.

Despite several attempts, the amount of deuterium incorporation could not be improved above 80%. However, the 20% non-deuterated starting material was taken into account in the calculation of the KIE by subtracting 0.20 from each integral of 1.00.

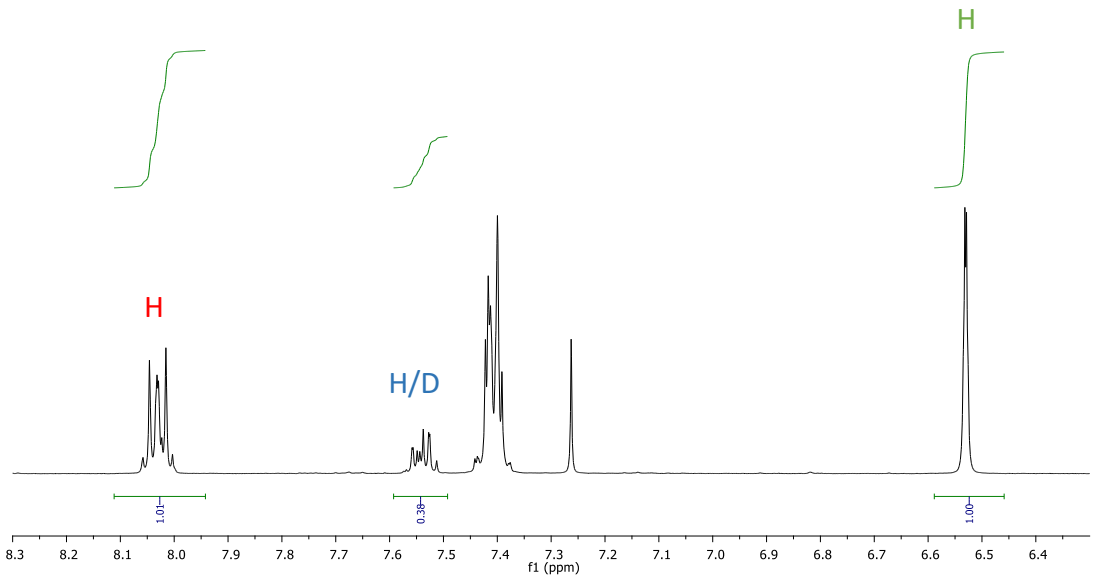
3-Bromo-6-methyl-4-(phenoxy-2-d)-2-pyrone (**152**) was reacted under the standard catalytic conditions[30] in an intramolecular competition KIE experiment (see **Section 4.1.1**).

It should be noted that no evidence of scrambling was observed under the standard reaction conditions. Scrambling is defined as a process whereby hydrogen atoms undergo intramolecular migration.[32] However, throughout this chapter, scrambling is used to describe H–D exchange, which may be intra- or intermolecular. Often, the net effect of scrambling is that the level of deuteration in a compound is altered by the reaction conditions.

The product of the reaction was purified by column chromatography and analysed by ^{1}H NMR spectroscopy. Each ^{1}H NMR signal arising from compound **153** was unambiguously assigned using 1D and 2D NMR spectroscopy. The integrals of the indicated protons were used to determine the KIE (**Figure 4.3**).



152 (80% D) **153**



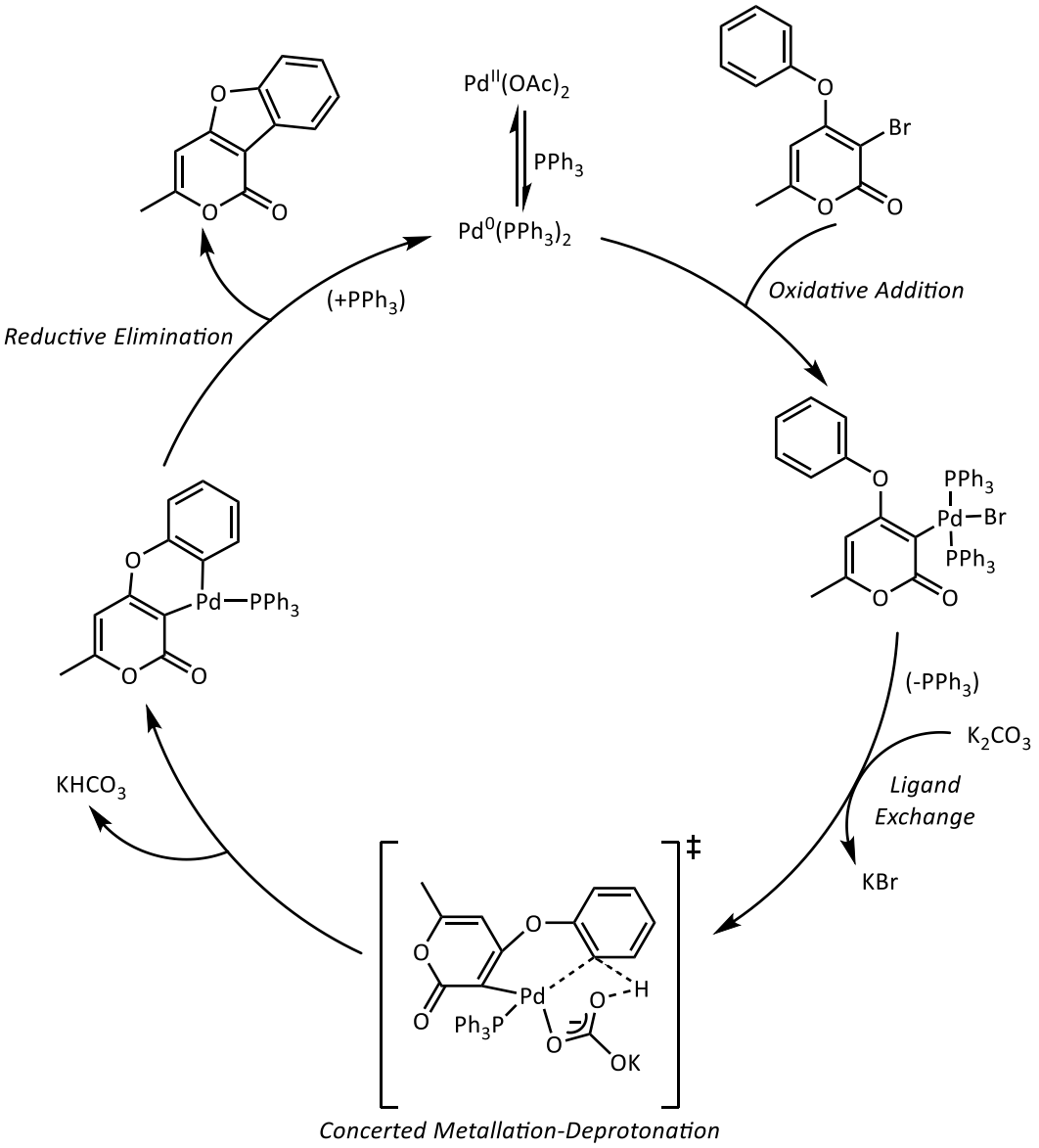
$$\mathrm{KIE} = \frac{k_H}{k_D} = \frac{\text{quantity of deuterated product}}{\text{quantity of non deuterated product}} = \frac{(1 - 0.20) - (0.38 - 0.20)}{(0.38 - 0.20)}$$

$$= \frac{(0.80 - 0.18)}{0.18} = \frac{0.62}{0.18} = 3.4$$

Figure 4.3. ^{1}H NMR spectrum and calculation for determination of KIE with substrate **152**.

This experiment was performed in duplicate. The first experiment (**Figure 4.3**) gave a KIE of 3.4, and the duplicate gave a KIE of 3.2. The average KIE was therefore 3.3. The observation of a KIE of 3.3 represents a kinetically significant C–H activation event (although not necessarily a rate-determining C–H activation step as discussed previously). This magnitude of KIE is typical of a CMD/AMLA mechanism, as reported in the literature.[7, 33] A CMD mechanism is proposed for this reaction (**Scheme 4.21**), where an initial oxidative addition into the C–3–Br bond is followed by ligand

exchange to form the key CMD transition state. An irreversible deprotonation followed by reductive elimination gives the product and regenerates the catalyst.

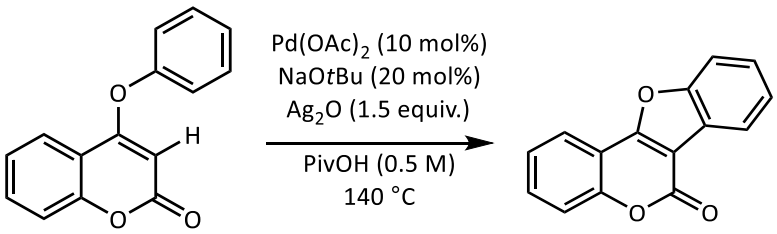


Scheme 4.21. Proposed mechanism for the intramolecular direct arylation of 3-bromo-4-phenoxy-2-pyrone.

4.4. Direct arylation *via* double C–H activation

Direct arylation which avoids one of the pre-activating groups by coupling a C–H and C–X bond is certainly progressive.[34-35] However, the idealised approach would involve the coupling of two C–H bonds.[36-37] When two unactivated species are coupled, it is often referred to as cross-dehydrogenative coupling (CDC).[36, 38-40] In particular, efforts have been focused on direct oxidative coupling between two aromatic C−H bonds.[41] This type of cross-coupling reaction is on the 'wanted list' of top pharmaceutical companies as a greener route to biaryls.[42] However, such processes are thermodynamically disfavoured (for example, the homocoupling of benzene to give biphenyl and dihydrogen is thermodynamically disfavoured by 13.8 kJ mol^{-1}),[43] and given that several sites are usually available for C–H activation in even the simplest organic molecules, regioselective oxidative coupling of this type is a daunting challenge.

Within the McGlacken group, conditions were developed which allowed the formation of tricyclic pyrones and coumarins by the coupling of phenoxy-substituted substrates *via* CDC (**Scheme 4.22**).[29, 44]



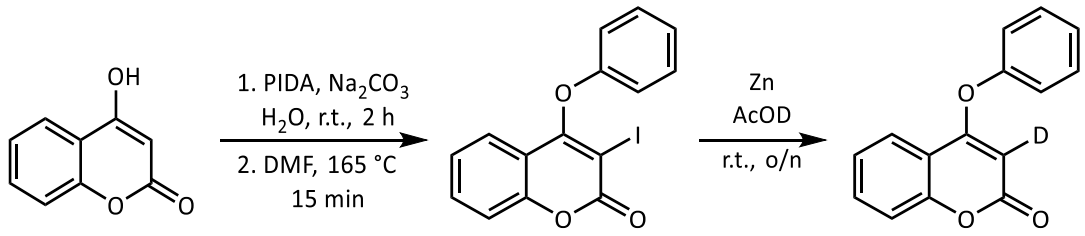
97 **154**

Scheme 4.22. Double C–H activation of 2-coumarin **97**.

Work on this section of the project involved the synthesis of a range of 2-coumarin substrates, including deuterated substrates, and subsequent investigation of both C–H activation events. These investigations involved reversibility studies and the determination of KIEs. Density Functional Theory (DFT) calculations were performed by our collaborator Prof. Zhenyang Lin at the Hong Kong University of Science and Technology. The experiments, results and interpretations will be discussed.

4.4.1. Synthesis of 2-coumarin substrates

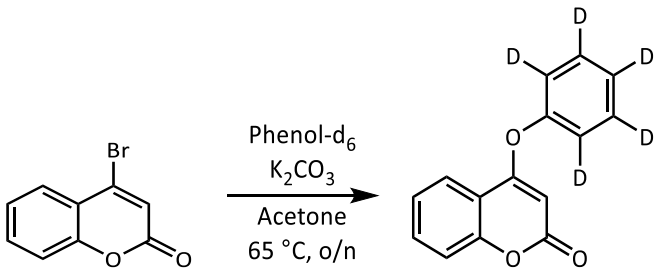
To allow the mechanistic investigations to be performed, a range of 2-coumarin substrates were synthesised. The preparation of 4-phenoxy-2-coumarin (**97**) is described in **Section 3.3.1**. A deuterated analogue of **97**, 3-deuterio-4-phenoxy-2-coumarin (**156**) was synthesised from 4-hydroxy-2-coumarin (**19**) (**Scheme 4.23**). 4-Hydroxy-2-coumarin (**19**) was treated with phenyliodo(III)diacetate (PIDA) in the presence of Na_2CO_3 to give a zwitterion, which, at 165 °C in DMF, underwent thermal rearrangement *via* a spiro-Meisenheimer complex to give 3-iodo-4-phenoxy-2-coumarin (**155**). 3-Iodo-4-phenoxy-2-coumarin (**155**) was purified by recrystallisation from MeOH and isolated in 38% yield over the two steps. Reductive deiodination in the presence of zinc and monodeuterioacetic acid gave 3-deuterio-4-phenoxy-2-coumarin (**156**) in 86% yield with 97% deuterium incorporation at the indicated position. The deuterium incorporation was measured using ^{1}H NMR spectroscopy, with a 0.03H integral at 5.41 ppm in the ^{1}H NMR spectrum confirming the quantity of deuterium present, and a triplet at 93.3 ppm in the ^{13}C NMR spectrum affirming the presence of deuterium.



19 **155**, 38% **156**, 86% (97% D)

Scheme 4.23. Synthesis of 3-deuterio-4-phenoxy-2-coumarin (**156**).

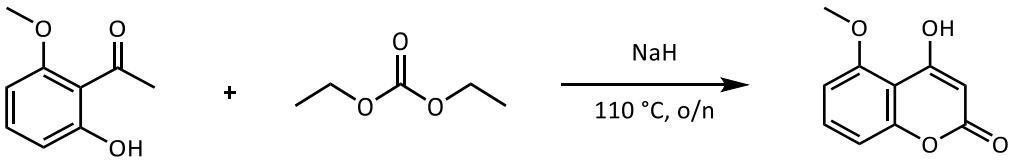
4-(Phenoxy-d_5)-2-coumarin (**157**) was synthesised from the reaction of 4-bromo-2-coumarin (**96**) and phenol-d_6 under basic conditions in acetone at 65 °C overnight (**Scheme 4.23**). After aqueous workup and washing with 10% aqueous NaOH, 4-(phenoxy-d_5)-2-coumarin (**157**) was isolated as a light brown solid in 86% yield. Deuterium incorporation was >99%.



96 **157**, 86%

Scheme 4.24. Synthesis of 4-(phenoxy-d_5)-2-coumarin (**157**).

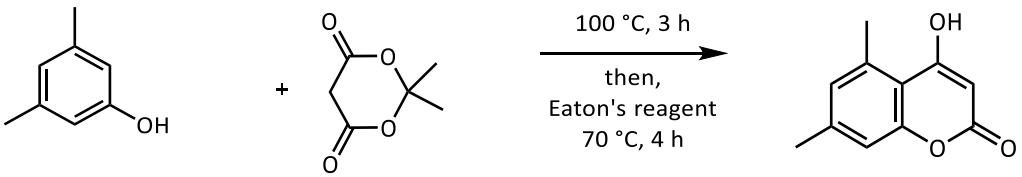
Two 2-coumarin substrates with substituted aryl backbones were required for the mechanistic studies which will be described later. To this end, the required 4-hydroxy-2-coumarins were synthesised. 4-Hydroxy-5-methoxy-2-coumarin (**159**) was synthesised from 2'-hydroxy-6'-methoxyacetophenone and diethyl carbonate in the presence of sodium hydride.[45-46] Purification by recrystallisation from EtOH gave 4-hydroxy-5-methoxy-2-coumarin (**159**) in 24% yield.



158, 74% **159**, 24%

Scheme 4.25. Synthesis of 4-hydroxy-5-methoxy-2-coumarin (**159**).

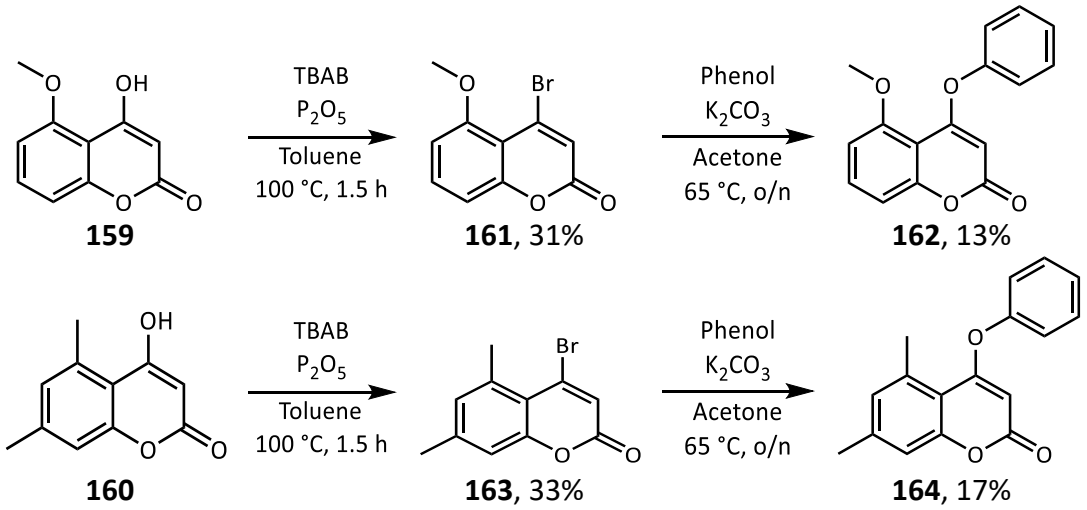
4-Hydroxy-5,7-dimethyl-2-coumarin (**160**) was synthesised from 3,5-dimethylphenol and Meldrum's acid.[47] The ester which formed was cyclised in the presence of Eaton's reagent to give 4-hydroxy-5,7-dimethyl-2-coumarin (**160**) in 78% yield after recrystallisation.



160, 78%

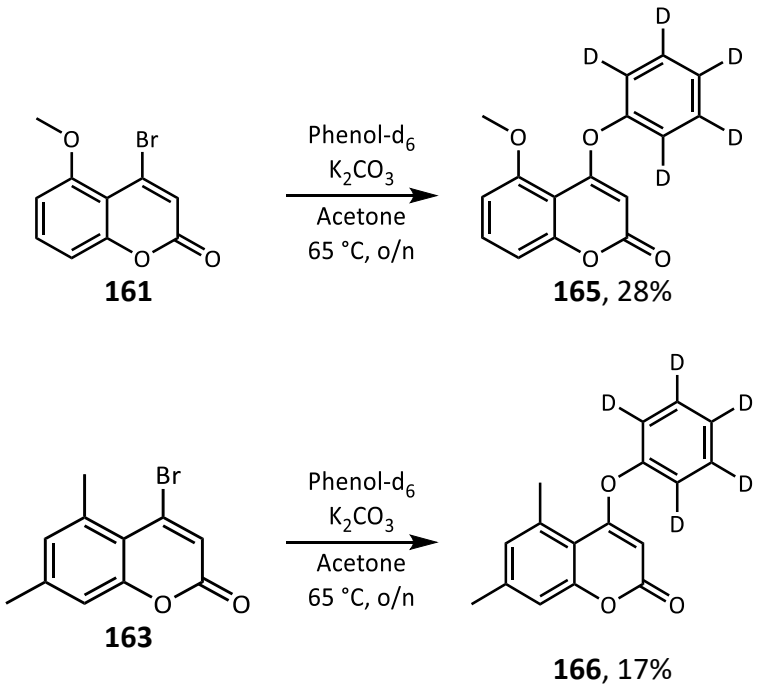
Scheme 4.26. Synthesis of 4-hydroxy-5,7-dimethyl-2-coumarin (**160**).

As before, the 4-hydroxy-2-coumarins were brominated with TBAB to give the 4-bromo-2-coumarins **161** and **163** in 31% and 33% yields respectively, which were in turn reacted with phenol under basic conditions to give the 4-phenoxy-2-coumarins **162** and **164**, in 13% and 17% yields respectively (**Scheme 4.27**).



Scheme 4.27. Synthesis of aryl substituted 4-phenoxy-2-coumarins **162** and **164**.

The corresponding penta-deuterated analogues were synthesised by reaction of the 4-bromo-2-coumarins with phenol-d_6, to give 4-(phenoxy-d_5)-5-methoxy-2-coumarin (**165**) in 28% yield and 4-(phenoxy-d_5)-5,7-dimethyl-2-coumarin (**166**) in 17% yield (**Scheme 4.28**). The yields for reactions at the 4-position when the 5-position is substituted are considerably lower than for the unsubstituted 2-coumarins. This is could be due to sterics or the effect of having electron-donating groups close to a reaction site which is required to be electrophilic.



Scheme 4.28. Synthesis of aryl substituted 4-(phenoxy-d_5)-2-coumarins **165** and **166**.

4.4.2. C–H Activation at C–3 of the 2-coumarin

For the investigation of the mechanism of the double C–H activation of substrate **97** to give cyclised product **154**, the C–H activation at C–3 of the 2-coumarin was examined in the first instance.

During the reaction, both the starting material **156** and the product **154** were carefully monitored by ^{1}H NMR spectroscopy. For starting material **156**, it was observed that the value of the integral for the C–3 proton at 5.41 ppm was increasing over time under the reaction conditions, corresponding to a decrease in deuterium incorporation at this position (**Figure 4.4**). After just 5 min of reaction time, the starting material was isolated and deuterium incorporation at this position had decreased from 97% to 89%. The reaction was then performed in the absence of palladium. In this experiment, the deuterium incorporation at C–3 was not affected by the reaction conditions. This is consistent with a reversible palladation of C–3 as part of the reaction mechanism.

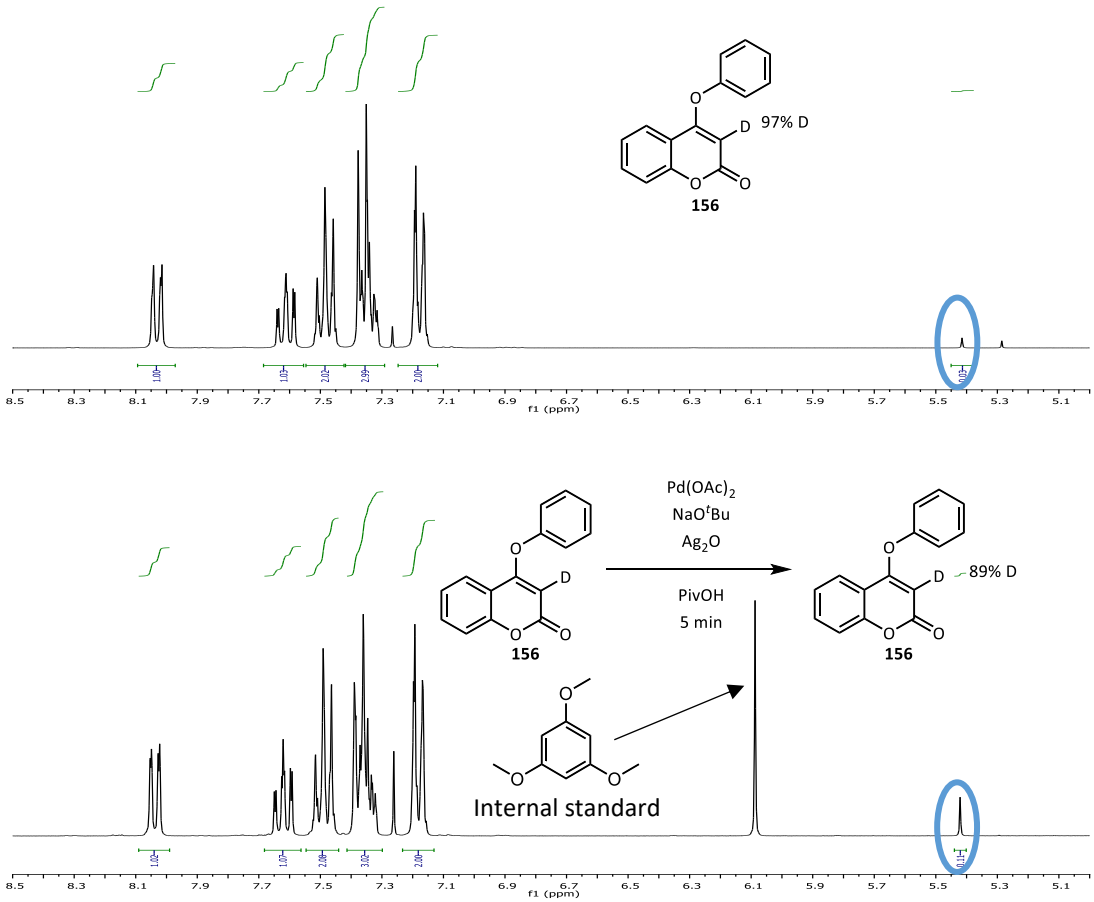


Figure 4.4. Reversible palladation at C–3 of 2-coumarin **156**.

The inverse reaction was performed using substrate **97** in monodeuterated pivalic acid (PivOD) (**Figure 4.5**). The peaks corresponding to H_a of product **154** and H of the starting material **97** overlap at 8.03 ppm. Since H_b integrates as 0.10 H, it can be inferred that H_a comprises 0.10 H of the 1.00 H integral at 8.03 ppm. Therefore, the integral for H of **97**/**156** works out to 0.90 H. If only the non-deuterated starting material **97** were present, then the integral for the singlet at 5.41 ppm would also be 0.90 H. However, since it integrates to 0.77 H, it can be said that the 3-deuterio-2-coumarin **156** is present. This showed deuterium incorporation exclusively at the C–3 position, confirming a reversible C–H activation event.

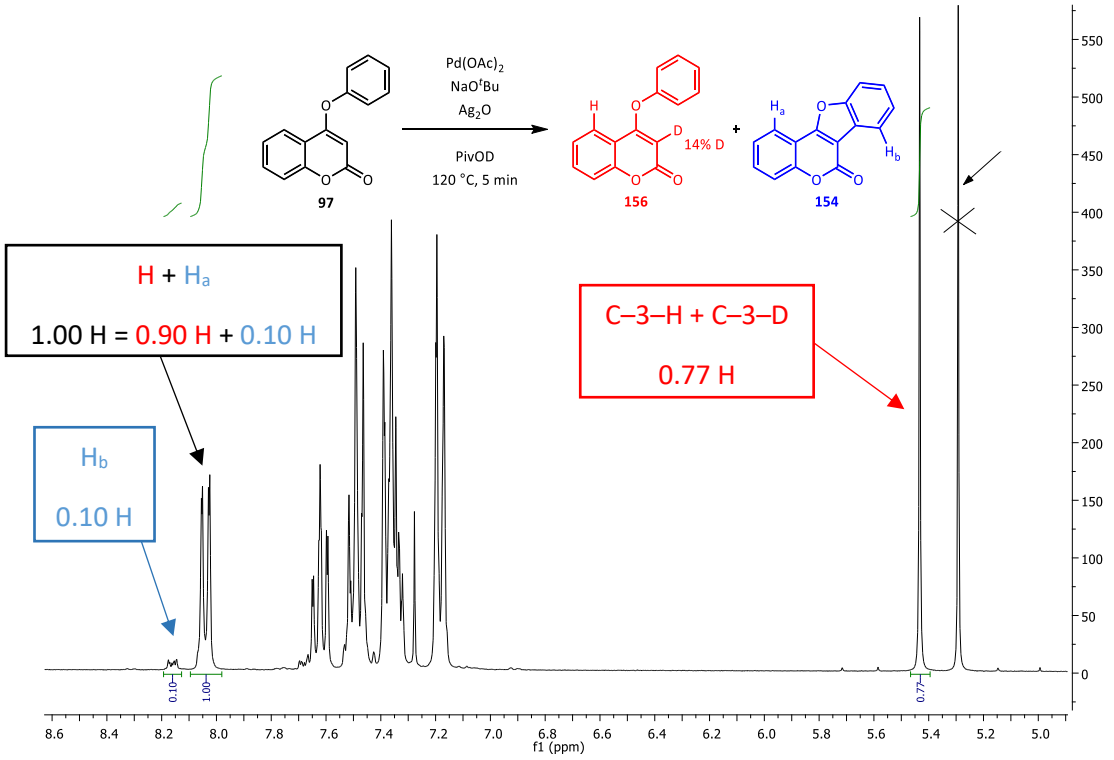


Figure 4.5. Reaction with PivOD.

Next, the rate of formation of product **154** from non-deuterated substrate **97** and deuterated substrate **156** in parallel reactions was compared (**Figure 4.6**).[19, 48] This method of KIE determination allows one to conclude whether the cleavage of a C–H bond is involved in the rate-determining step of a reaction.[4] The reaction was performed at 120 °C rather than the optimised 140 °C so that the reaction would progress slightly slower, to conveniently facilitate reaction monitoring. Interestingly, an induction period can be observed in the first 15 min of the reaction, which could be a key pre-catalyst to catalyst step, such as ligand dissociation/association to form the active Pd(II) species. The rate of product formation was observed to be very similar for the two substrates (**Figure 4.6**).

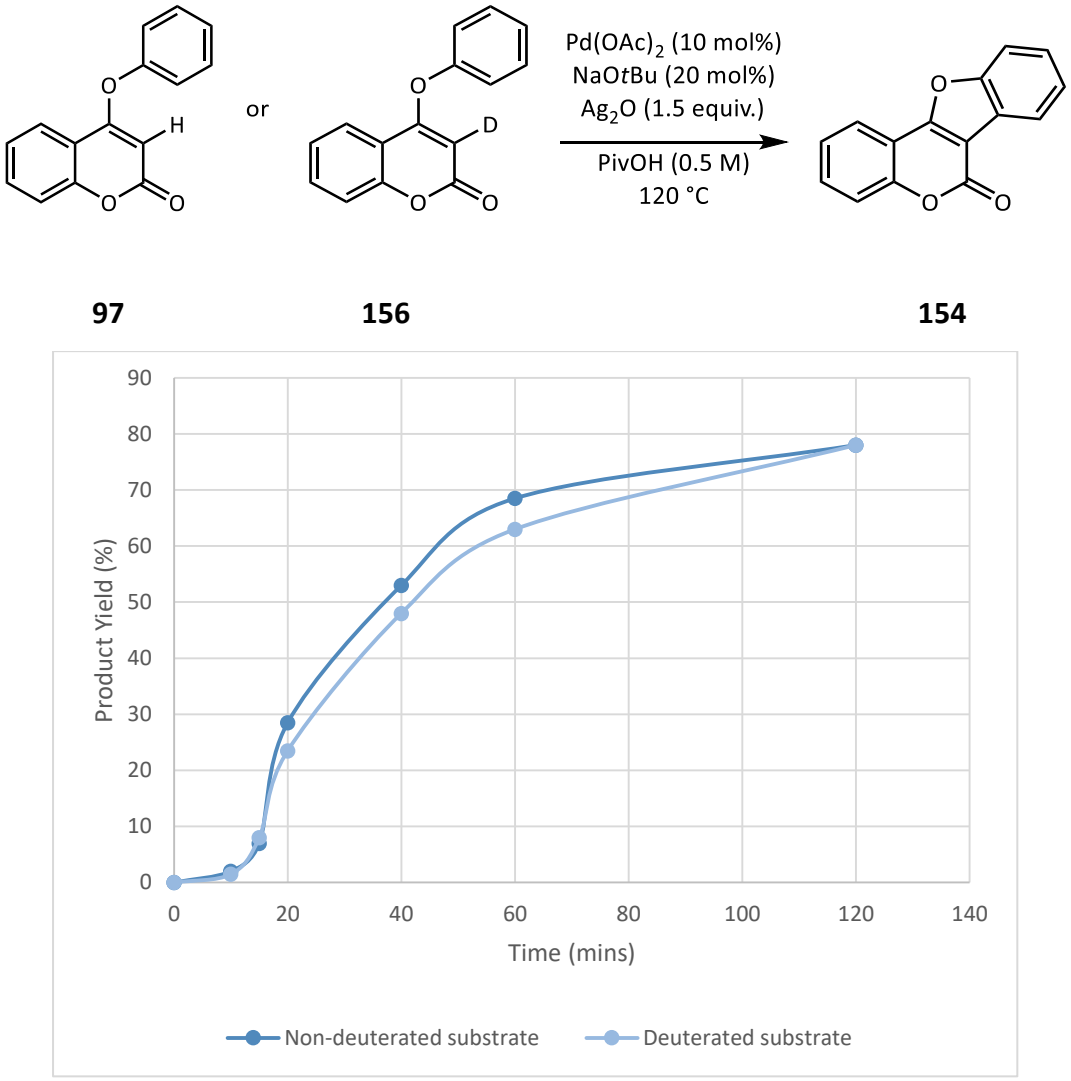
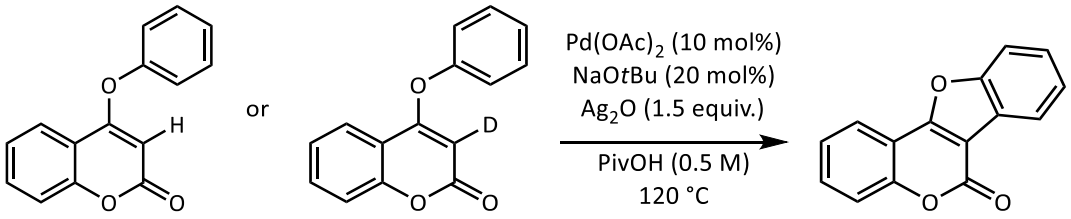
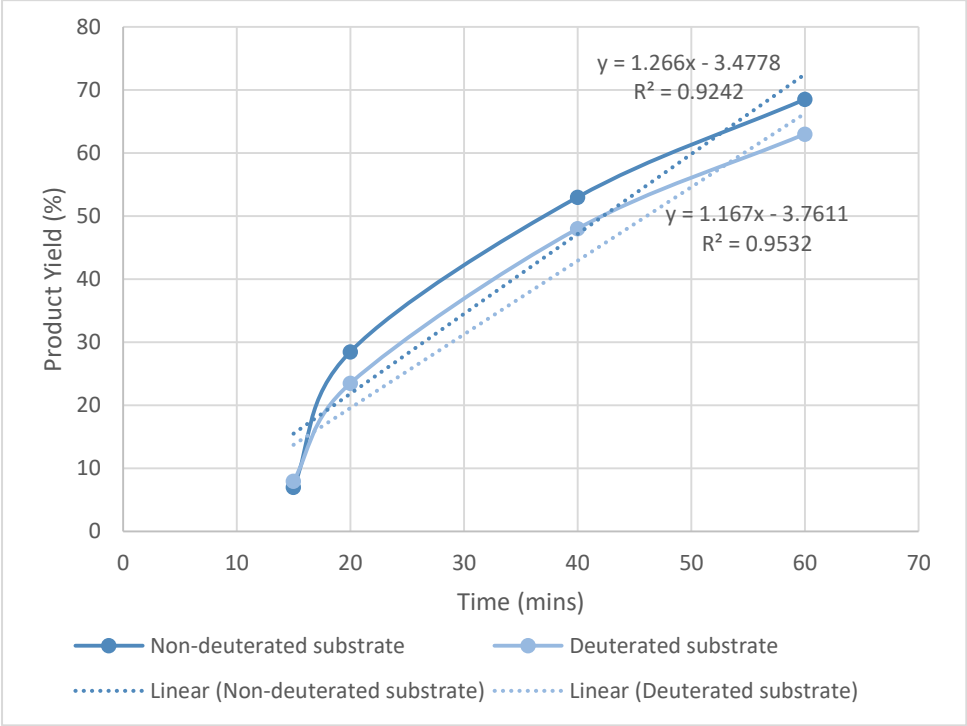


Figure 4.6. Reaction profile for the formation of product **154** from **97** and **156**.

The induction period is excluded from the calculation of the slope as it is the same for both substrates. The initial rates method was used to determine the KIE (**Figure 4.7**).[19]



97 **156** **154**



$$\text{KIE} = \frac{k_H}{k_D} = \frac{m_1}{m_2} = \frac{1.266}{1.167} = 1.08$$

Figure 4.7. The initial rates method for KIE determination.

A KIE of ~1 indicates that the rate-determining step of the reaction does not involve cleavage of the C–H bond at the C–3 position of 2-coumarin **97**.[4]

4.4.3. C–H Activation of the aryl ring

In our investigation of the mechanism of the double C–H activation of substrate **97** to give product **154**, the C–H activation of the aryl ring was next to be examined.

Initially, determination the KIE using the initial rates method was desired, similar to the technique used for the C–3 position. To this end, compound **157** was subjected to the reaction conditions to determine the effect of penta-deuteration on the rate of reaction (**Figure 4.8**).

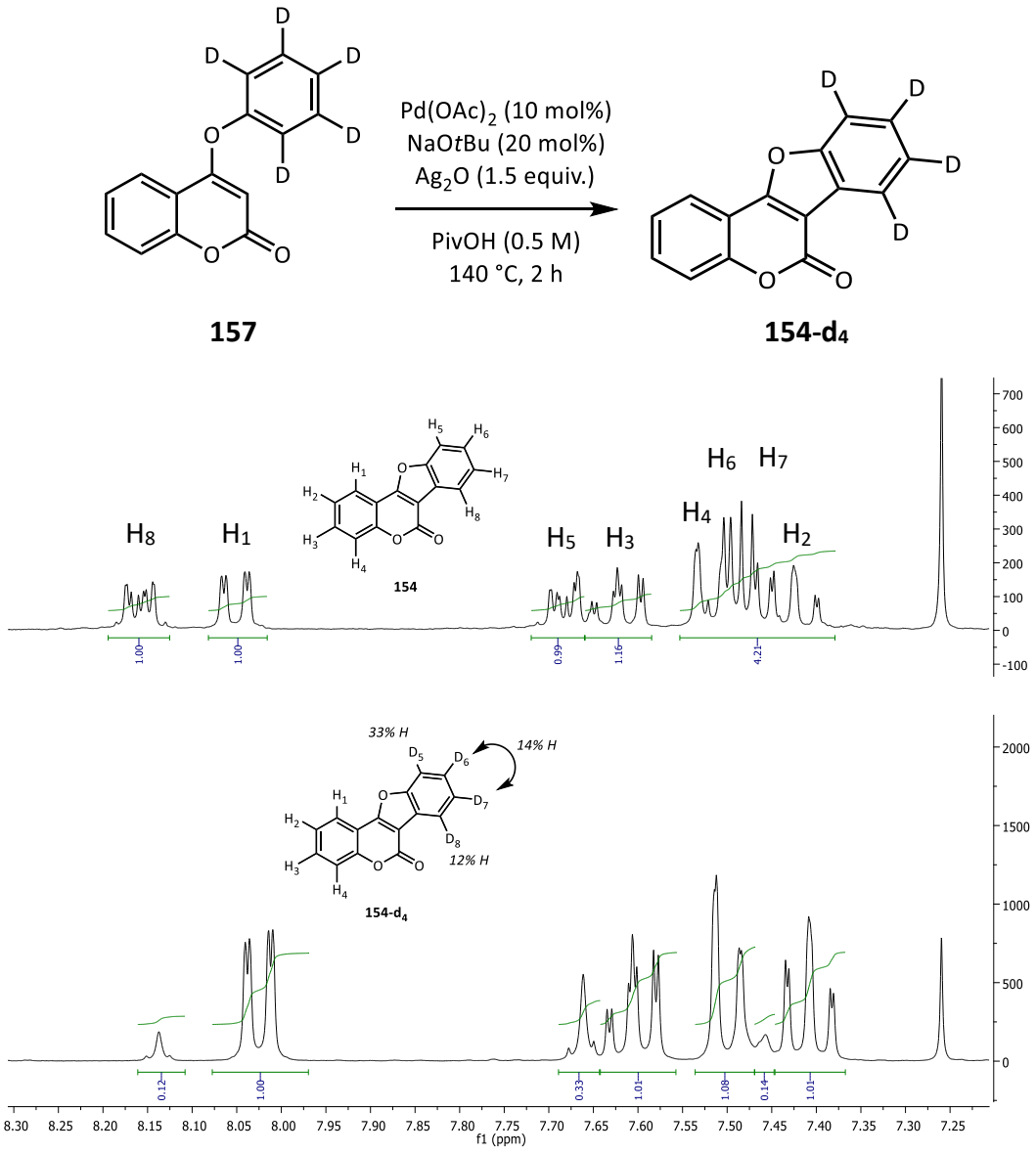
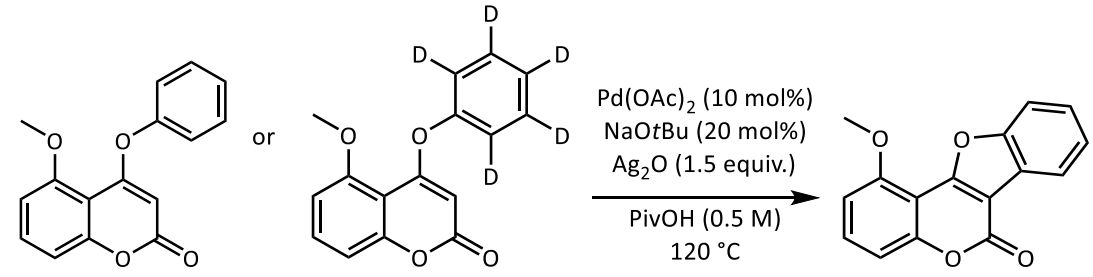


Figure 4.8. Scrambling of deuterium in the reaction of substrate **157**.

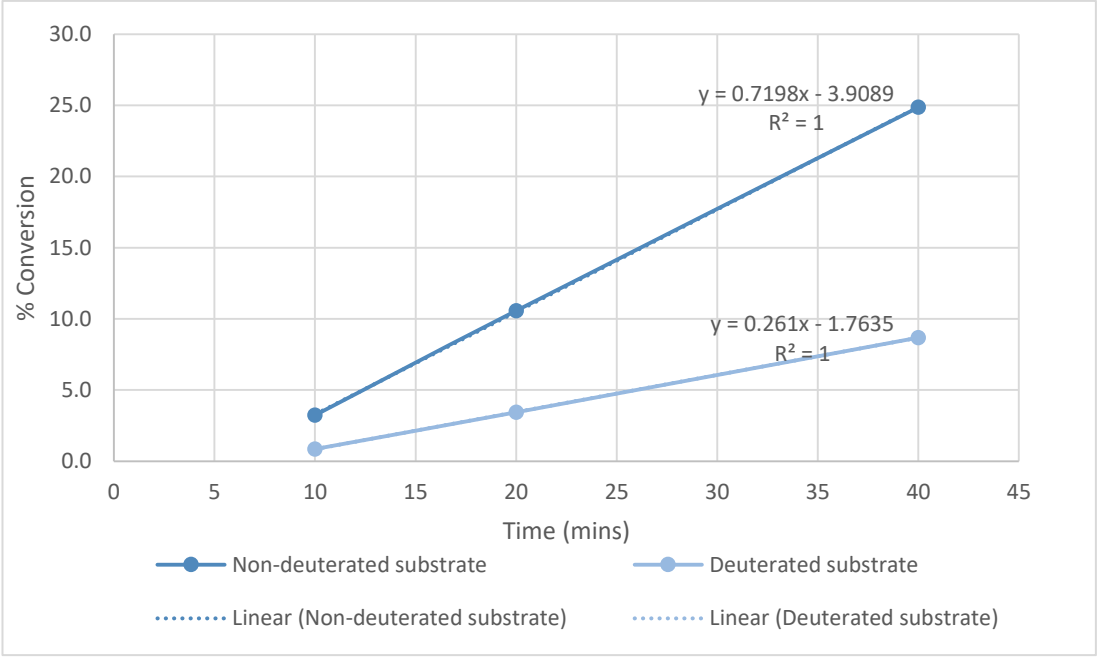
Surprisingly, unexpected peaks were observed in the ^{1}H NMR spectrum of the crude reaction mixture. The peaks persisted after silica gel chromatography of product **154-d$_4$**. It became clear that these peaks were the result of deuterium being exchanged for hydrogen, or scrambling, in the product. The extent of hydrogen incorporation at D–5 was found to be 33%, which indicates that the *ortho* position is most amenable to C–H activation. A total of 14% hydrogen incorporation was attributed to D–6 and D–7, as indicated in **Figure 4.8**. The 12% hydrogen incorporation at the D–8 position is believed to be caused by directed (C=O) C–H activation after the product is formed.

Scrambling appears early in the course of the reaction. However, even after the starting material is fully consumed, **154** itself can undergo further scrambling under these reaction conditions. This was confirmed by performing the same reaction with substrate **157** again, but leaving it on for 16 h. Analysis by ^{1}H NMR spectroscopy showed that the level of hydrogen incorporation at positions D–5 to D–8 was increased compared to the level of hydrogen incorporation after 2 h.

This scrambling presented other problems. Since there are no integrals unique to cyclised product **154-d$_4$** which allow for delineation from the starting material **157** and baseline-to-baseline integration, the system is unsuitable for use in determining the KIE using parallel reactions with ^{1}H NMR spectroscopy as the method of measurement. A clear integral that is unique to each of the starting materials and products (deuterated and non-deuterated) is required for this technique. To circumvent this issue, 5-methoxy-2-coumarin **162** and its deuterated analogue **165** were utilised. When subjected to the reaction conditions, these substrates give product **167** and its deuterated analogue. Since the 5-methoxy group is unlikely to participate in a C–H activation process, the ^{1}H NMR signals corresponding to this group allowed the progress of the reaction to be monitored using ^{1}H NMR spectroscopy. The 3H integral corresponding to the 5-methoxy peak shifts downfield significantly for the product compared to the starting material (3.93 ppm for starting material **162** and at 4.11 ppm for product **167**). As before, the induction period is excluded from the calculation of the slope as it is the same for both substrates. The experiment was performed by comparing the conversion of substrate **162** and **165** to product **167** (and its deuterated analogue) in parallel reactions. The initial rates method was used to determine the KIE (**Figure 4.9**).[19]



162 **165** **167**

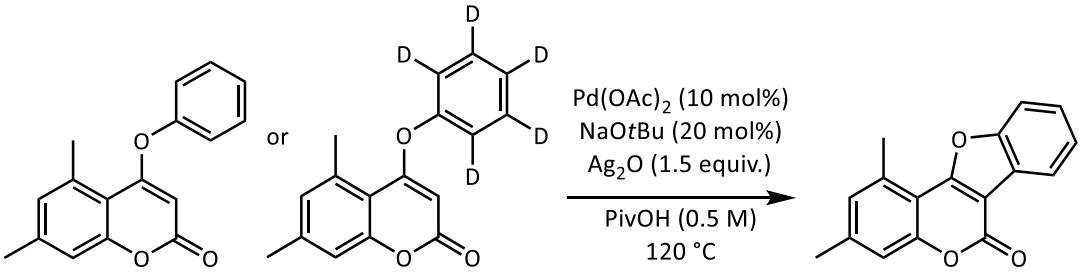


$$\text{KIE} = \frac{k_{\text{H}}}{k_{\text{D}}} = \frac{\text{m}_1}{\text{m}_2} = \frac{0.7198}{0.261} = 2.76$$

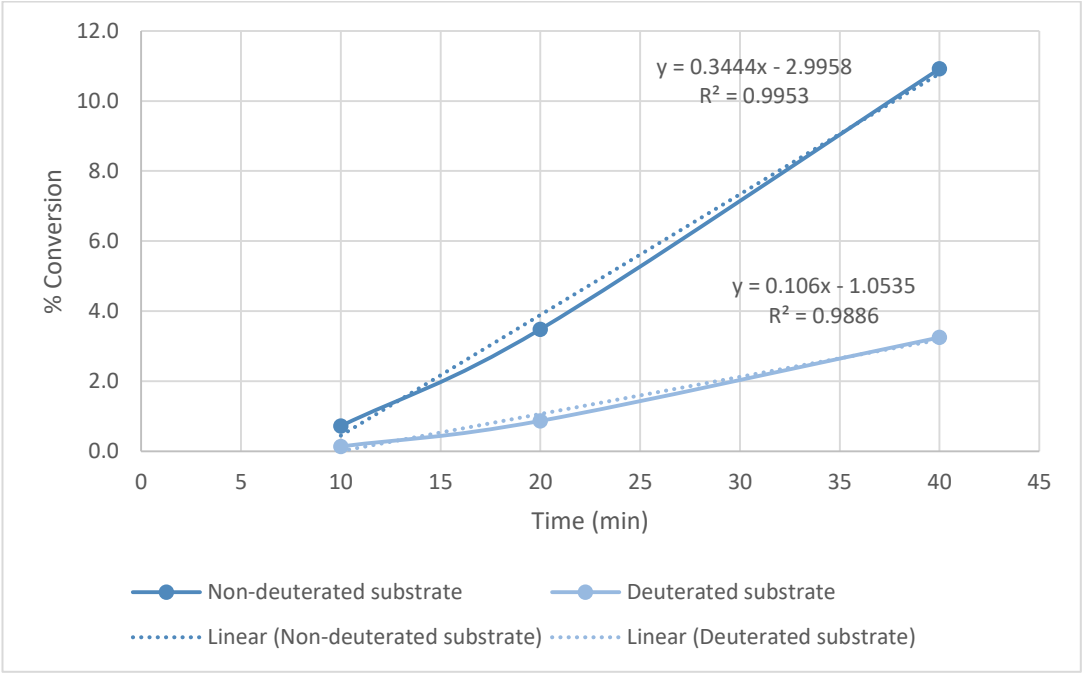
Figure 4.9. The initial rates method for KIE determination.

The KIE was determined to be 2.76 from this method. This method of calculation is accurate because the 5-OMe group is not affected by scrambling, and so the value of that integral is reliable. The determination of a positive KIE by this method confirms that C–H bond cleavage on the aryl ring is involved in the rate-determining step of this reaction mechanism.[4]

To confirm the KIE, the same experiment was performed with the 5,7-dimethyl-2-coumarin substrate **164** and the corresponding penta-deuterated substrate **166** (**Figure 4.10**).



164 **166** **168**



$$\text{KIE} = \frac{k_{\text{H}}}{k_{\text{D}}} = \frac{\text{m}_1}{\text{m}_2} = \frac{0.3444}{0.106} = 3.25$$

Figure 4.10. The initial rates method for KIE determination.

The KIE was determined to be 3.25 from this experiment, which is in good agreement with the KIE of 2.76 determined using the 5-OMe substrates, giving a positive KIE of approximately 3.

It was necessary to use conversion values for the KIE experiments shown in **Figure 4.9** and **Figure 4.10**, rather than yields determined by quantitative ^{1}H NMR spectroscopy, due to low yields in the synthesis of substrates. To ensure that this was a robust method, the KIE determination shown in **Figure 4.7** was calculated using conversion values rather than yield, and the KIE result was similar.

The determination of a positive KIE (approx. 3) by both of initial rate experiments is good evidence that C–H bond cleavage on the aryl ring is involved in the rate-determining step of this reaction mechanism.[4]

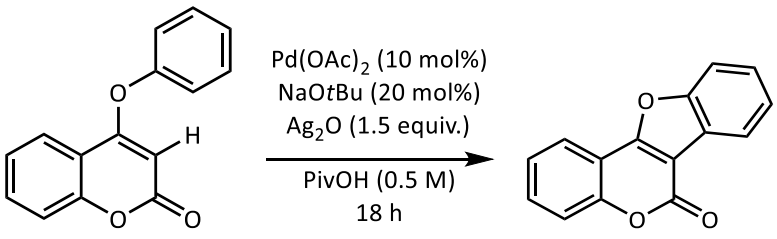
4.4.4. Monitoring of double C–H activation by NMR

It was then planned to monitor the progress of the double C–H activation by NMR spectroscopy with the assistance of the UCC NMR spectroscopist, Dr. Lorraine M. Bateman. The probe on the 500 MHz spectrometer in the School of Chemistry can be heated to and held at a maximum temperature of 80 °C. It was planned to perform the reaction in an NMR tube in the spectrometer, and monitor the reaction by recording multiple spectra over several hours.

To this end, a series of control experiments were undertaken to determine if this was a viable method of investigation.

First, it was examined whether the reaction could be run at lower temperatures than those reported in our methodology paper (**Table 4.3**).[44]

Table 4.3. Investigation of effect of lower temperature on double C–H activation reaction.



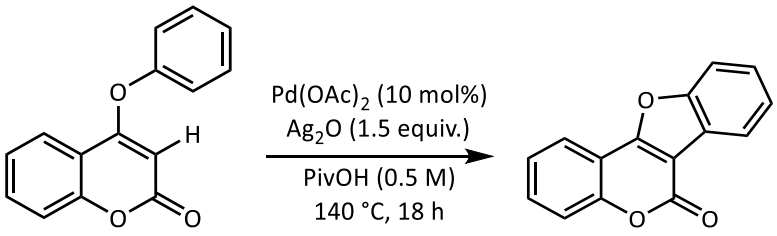
97 **154**

Reaction Temperature (°C)	Conversion (%)
40	0
60	4
80	65

These results revealed that the reaction would not progress at temperatures below 60 °C, and that the reaction proceeds much slower at 80 °C than at 140 °C (as expected). However, it was hoped that the slower reaction would facilitate the NMR

monitoring study, and possibly allow the observation of reaction intermediates, such as those involving C–Pd bonds.

Next, the effect of excluding the base was investigated (**Scheme 4.29**).

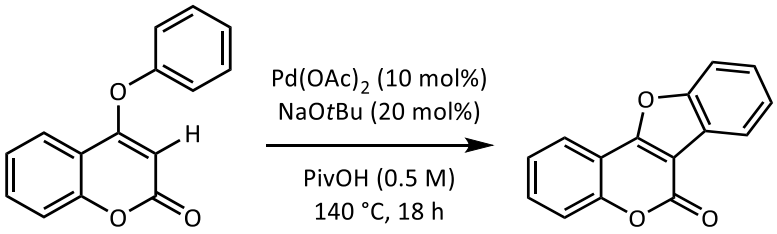


97 **154**, 63%

Scheme 4.29. Effect of excluding base from the reaction mixture. Yield determined from the ^{1}H NMR spectrum of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard for quantification.

Surprisingly, the reaction proceeded to 100% conversion in the absence of NaO*t*Bu, and a 63% yield was determined from the ^{1}H NMR spectrum of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard for quantification. No other species except for product **154** was identified in the ^{1}H NMR spectrum of the crude reaction mixture. For comparison, a yield of 92% was found in the presence of NaO*t*Bu.[44] Fagnou and co-workers also observed that the addition of substoichiometric amounts of base resulted in enhanced yields.[49] It may be that NaO*t*Bu has a role in the activation of the catalyst, as was recently reported by Docherty *et al.* for the activation of earth-abundant metals.[50] Alternatively, NaO*t*Bu may act as a proton shuttle, as previously discussed.[7]

Thirdly, the effect of excluding Ag_2O from the reaction mixture was studied (**Scheme 4.30**). It was found that the reaction proceeds to 26% conversion, which is 2–3 turnovers of the catalyst. This shows that at least some of the catalyst is oxidised back to Pd(II), possibly by air or some other internal oxidant. This could prove useful in further development of this reaction, as the use of stoichiometric silver salts to oxidise the catalyst is not cost-effective.



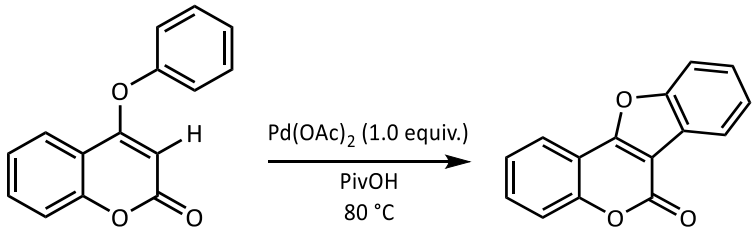
97 **154**

26% conversion

Scheme 4.30. Effect of excluding oxidant from the reaction mixture.

The results from the control experiments informed our decision to conduct an initial reaction in an NMR tube at 80 °C with a stoichiometric quantity of palladium, without NaO*t*Bu or Ag_2O. Stoichiometric palladium was used for two reasons. Firstly, it would maximise the possibility of observing some palladated intermediate of the catalytic cycle, and secondly, it would allow the reaction to proceed to completion without the silver salt. The NMR tube selected for this study was used with a coaxial insert. The coaxial insert contained DMSO-d_6. The use of a deuterated solvent such as DMSO-d_6 allows the spectrometer to establish a lock signal. This mitigates against the possibility of field drift over the time course of the experiments. The ^{1}H NMR signals arising from PivOH appear as a 9H singlet at 1.11 ppm, and a 1H singlet at 11.84 ppm. These signals are far from the area of interest (4.5–9.5 ppm) in the ^{1}H NMR spectrum.

The reagents were added into an NMR tube as per **Scheme 4.31**, and a coaxial insert containing DMSO-d_6 was placed in the NMR tube also. A series of spectra were obtained.



97 **154**

0% conversion

Scheme 4.31. Monitoring of double C–H activation reaction at 80 °C in 500 MHz spectrometer.

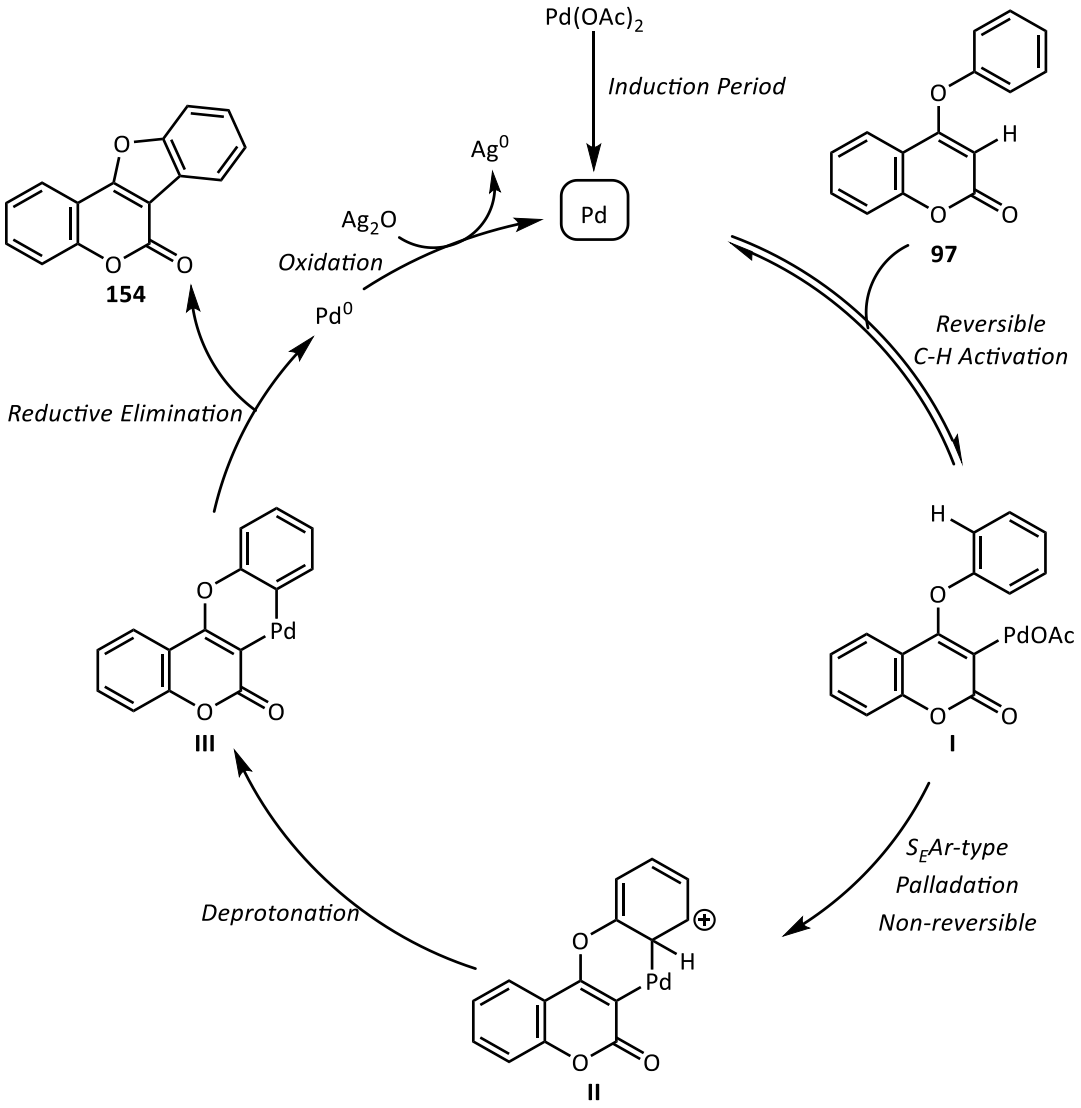
Unfortunately, the reaction did not progress even after a prolonged period of time. This was likely due to the consistency of the reaction mixture. The paste-like material was not sufficiently agitated by the spinning of the sample in the spectrometer.

Finally, it was decided to conduct the reaction under the same conditions (**Scheme 4.31**), but in a reaction tube with stirring at 120 °C. Samples were removed at various time points, cooled to 80 °C and the spectra of those samples at were recorded at 80 °C in the 500 MHz spectrometer using the coaxial insert containing DMSO-d_6. While the reaction did progress in this case, only starting material **97** and product **154** were observed in the recorded spectra. Disappointingly, no new peaks which could correspond to a palladated intermediate were identified.

4.4.5. Mechanistic Proposals

Initial proposal

An initial mechanistic proposal was made in our methodology paper (**Scheme 4.32**).[44] This was based on the data available at the time of publication, *i.e.* H/D exchange at C–3–H which demonstrates reversible, palladium-mediated C–H bond cleavage (**Figure 4.4** and **Figure 4.5**), and a non-significant KIE of 1.08 for the cleavage of the C–3–H bond (**Figure 4.7**). These experiments did not allow unambiguous determination of the mechanism of this reaction and shed little light on the mechanism of C–H activation of the aryl ring. However, an S_EAr mechanism (**Scheme 4.32**) was suspected at that stage. The absence of any scrambling on the aryl ring of starting material **157** suggested non-reversibility of that C–H cleavage step. An S_EAr step would account for this observation.



Scheme 4.32. Initial mechanistic proposal.

In our methodology paper, a reversible palladation of the C–3–H bond was proposed as the first step, giving **I**. This was supported by the observation that in the reaction of 4-phenoxy-2-coumarin (**97**) in PivOD, only deuterium incorporation at C–3 was observed in the starting material (**Figure 4.5**). Additionally, the level of deuterium incorporation at C–3 of 3-deuterio-4-phenoxy-2-coumarin (**156**) decreased under the reaction conditions (**Figure 4.4**). These two experiments indicated that activation of the C–3–H bond could be the first C–H activation event, and that it was likely to be reversible. A non-significant KIE of 1.08 (**Figure 4.7**) showed that C–3–H bond activation was not involved in the rate-determining step.

An S_EAr-type step was envisaged next to give intermediate **II**. S_EAr-type mechanisms have been proposed by Tunge and Foresee for the hydroarylation of alkenes and alkynes,[51] and by Shi and Buchwald for the synthesis of substituted 3,3-difluoro-2-oxindoles *via* intramolecular C–H difluoroalkylation.[52] Such S_EAr-type mechanisms include an electrophilic palladation of the aryl ring, *i.e.* the electrophilic palladium catalyst activates the unsaturated system towards nucleophilic attack by the arene to form a Wheland intermediate (**II**). The final steps were proposed to involve irreversible deprotonation (to give **III**) and reductive elimination to afford the product (**154**).[44] However, a CMD mechanism[7, 11-12, 33] for activation of both C–H bonds was also considered possible.

Revised proposal

The subsequent observation of a primary positive KIE of 3 (**Figure 4.9** and **Figure 4.10**) showed that our mechanistic proposal in the methodology paper was correct for step 1 (C–H activation at C–3), but incorrect for step 2 (C–H activation of the aryl ring). In an S_EAr-type mechanism, the palladation is the rate-determining step, but the C–H bond cleavage to restore aromaticity is fast. Since a positive KIE was observed for the cleavage of the aryl C–H bond, a Wheland intermediate (**Scheme 4.32**, **II**) cannot be evoked, and therefore the mechanism of aryl C–H bond activation cannot involve S_EAr-type steps.

With this additional information, the experimental data gathered to date shows that:

1. The C–3–H bond cleavage is palladium-mediated, reversible and not involved in the rate-determining step.

2. The aryl C–H bond cleavage is involved in the rate-determining step.

At this stage, we engaged with a collaborator, Prof. Zhenyang Lin of the Hong Kong University of Science and Technology, to carry out DFT(ωB97X-D) calculations to gain further mechanistic insights. The pathway for the CDC of 4-phenoxy-2-coumarin **97** was calculated (**Figure 4.11**).

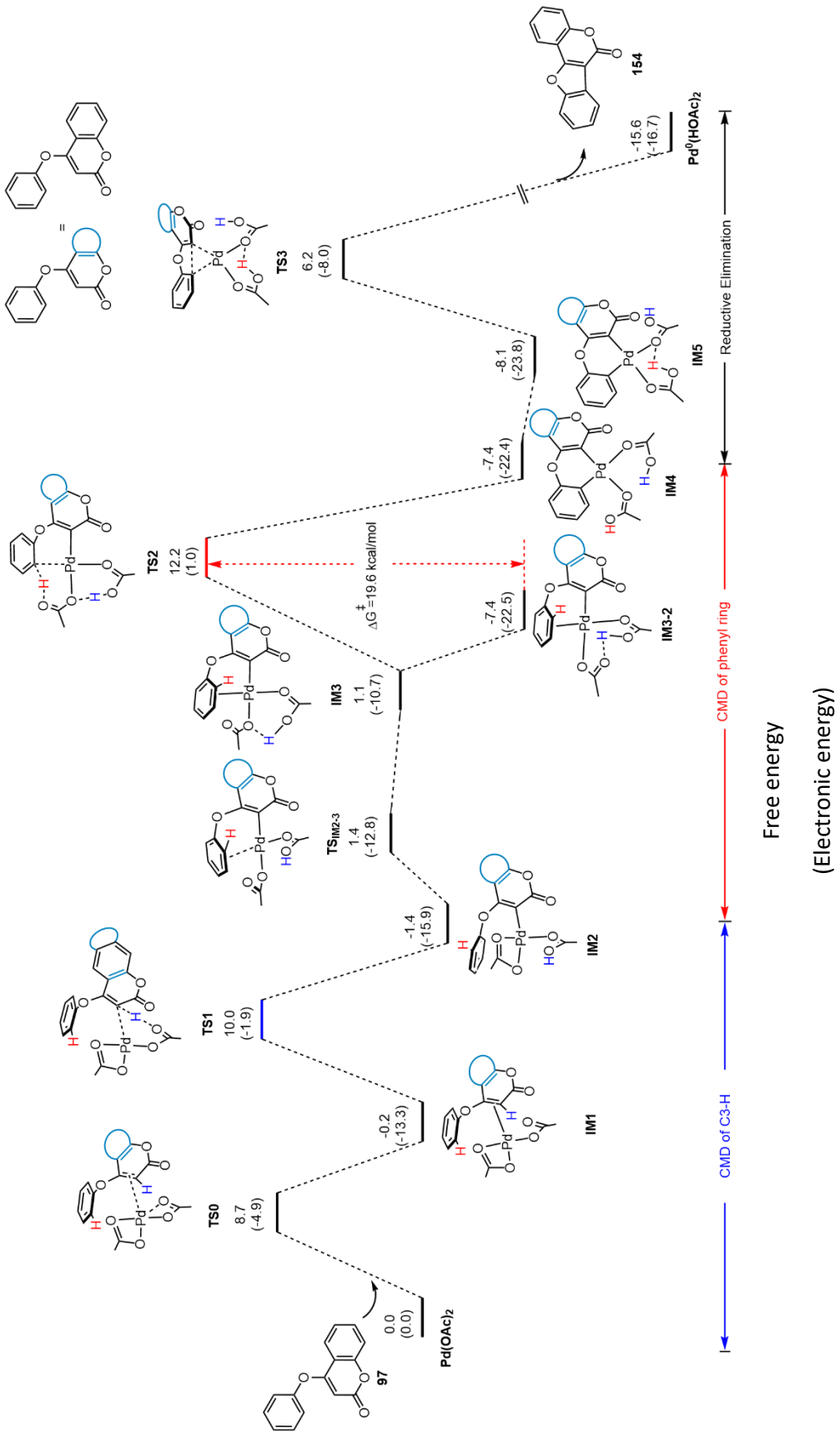


Figure 4.11. DFT calculations for the direct arylation of **97** to **154** *via* double C–H activation. Pathway shows that CMD of C–3–H bond happens first.

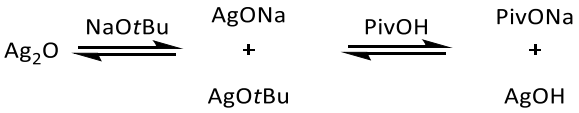
The first step of the reaction pathway was calculated to be a κ^2-κ^1 displacement of an acetate ligand (**TS0**, $\Delta G^{\ddagger}$ = 8.7 kcal mol^{-1}) to give a π-complex **IM1**, which progresses through the CMD transition state (**TS1**, $\Delta G^{\ddagger}$ = 10.2 kcal mol^{-1}) to give **IM2**. The abstraction of the proton at C–3 could be reversible due to the similarity of the free energies of the starting material (ΔG = 0.0 kcal mol^{-1}), **IM1** (ΔG = −0.2 kcal mol^{-1}) and **IM2** (ΔG = −1.4 kcal mol^{-1}). This correlates well with the experimentally observed ease of deuterium abstraction (**Figure 4.4**) and incorporation (**Figure 4.5**). Additionally, the initial activation of the C–3–H bond of the 2-coumarin is not turnover-limiting, which is consistent with the observed KIE of 1.08 for the isotopic substitution of this bond (**Figure 4.7**).

From **IM2**, a π-complex (**IM3**) is formed *via* $\mathbf{TS_{IM2\text{-}3}}$. **IM3** could then interconvert to **IM3-2** ($\Delta G^{\ddagger}$ = −8.5 kcal mol^{-1}). **IM3-2** (ΔG = −7.4 kcal mol^{-1}) contains a stronger hydrogen bond and is calculated to be more stable than **IM3** (ΔG = 1.1 kcal mol^{-1}). The summit of the potential energy surface, *i.e.* the turnover-limiting step, for the pathway is the activation of the aryl C–H bond *via* **TS2** ($\Delta G^{\ddagger}$ = 19.6 kcal mol^{-1}) to **IM4**. This is consistent with the experimentally observed KIE of approx. 3 for the cleavage of the aryl C–H bond.

IM4 is calculated to isomerise to the lower energy **IM5** through the formation of a hydrogen bond between the two acetate ligands. Reductive elimination of $Pd(HOAc)_2$ from **IM5** to give product **154** proceeds through **TS3** ($\Delta G^{\ddagger}$ = 14.3 kcal mol^{-1}). The reductive elimination is relatively facile, and product **154** (ΔG = −15.6 kcal mol^{-1}) is lower in energy than **IM5** (ΔG = −8.2 kcal mol^{-1}). This indicates that the activation of the aryl C–H is irreversible.

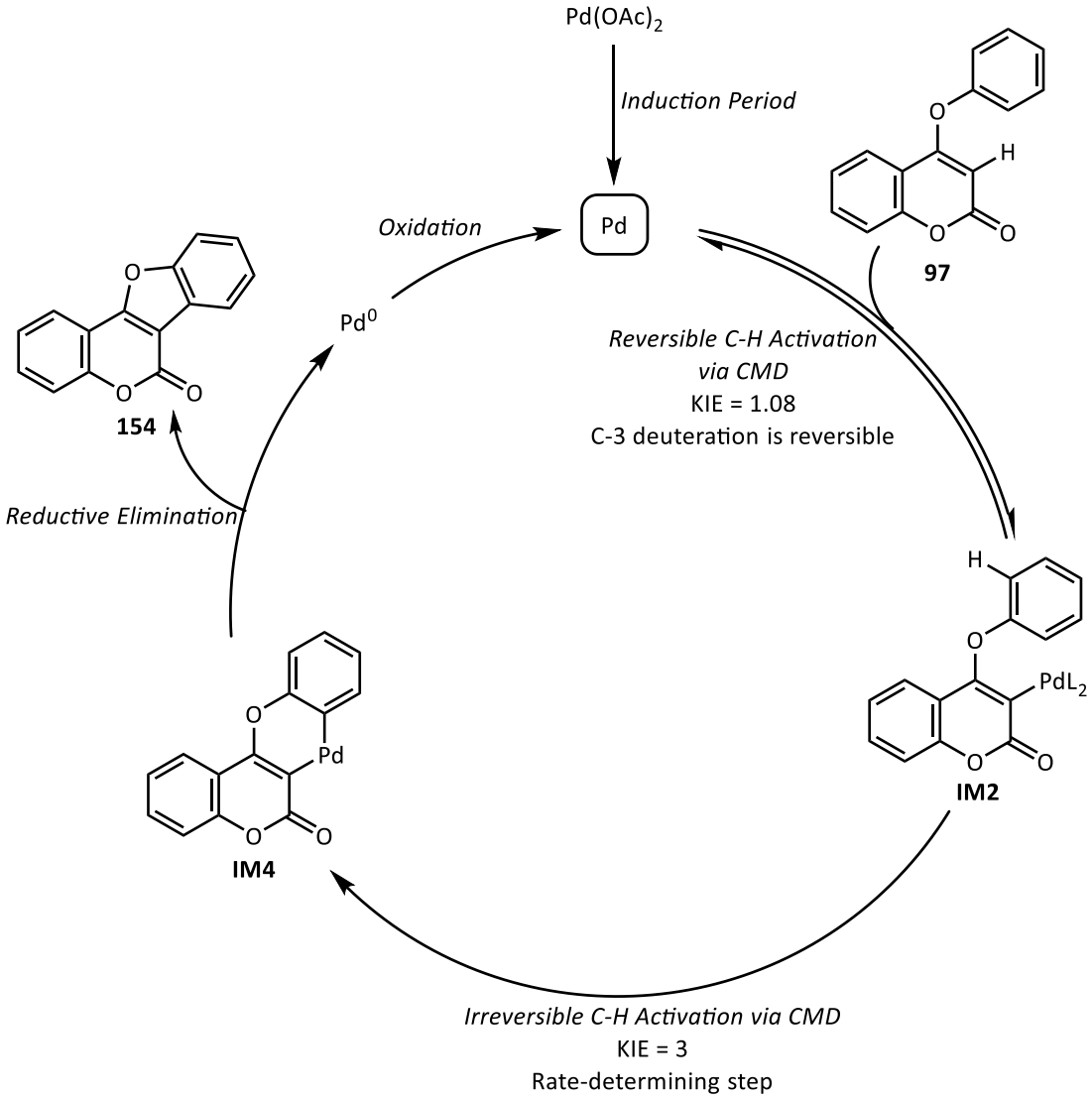
The protons on the acetic acid ligands of $Pd(HOAc)_2$ could transfer to a Brønsted base such as *tert*-butoxide (*t*BuO$^-$) or pivalate (PivO$^-$). One or more silver species could act as an insoluble proton sink, similar to the proposed role of the carbonate bases discussed in **Section 4.2** and **Section 4.3**. Finally, Pd(0) is likely oxidised to Pd(II) by Ag_2O.

The true nature of the active catalytic and deprotonating species are not fully understood. It is difficult to study the role of Ag_2O and related species in a meaningful way using DFT calculations as there are no reasonable structural models for Ag_2O at this time. However, it would be reasonable to postulate that a number of equilibria, such as those shown in **Scheme 4.33**,[53] could exist in the reaction mixture. The presence of numerous basic species could offer an explanation for why the starting material **97** was fully consumed and a 63% yield of product **154** was measured in the absence of NaO*t*Bu (**Scheme 4.29**).



Scheme 4.33. Some potential species in the reaction mixture which were not modelled.

In conclusion, the catalytic reaction detailed in **Scheme 4.34** is considered most likely. It comprises of an initial reversible CMD of the C–3–H bond of 2-coumarin followed by irreversible, turnover-limiting CMD of the aryl C–H bond. Reductive elimination of Pd(0) gives the product, and deprotonation and oxidation of the Pd(0) back to the active catalyst Pd(II) likely completes the catalytic cycle. The experimental evidence is consistent with the DFT calculations. C–H activation at the C–3 position of the 2-coumarin substrate (**97** to **IM2**) was calculated to be reversible because the barrier for the reverse reaction was lower than the barrier for the forward reaction to **IM4**. This is supported by the observation of Pd-mediated H–D exchange at that position. A KIE of 1.08 was observed for the cleavage of the C–3–H bond, showing that this was not the RDS of the reaction. The DFT calculations also show that this is not the RDS. Instead, cleavage of the aryl C–H bond was calculated to be the highest energy transition state of the reaction coordinate diagram (**TS2**), which is consistent with the experimentally observed isotope effect of 3. Further study will be required to fully elucidate the roles of NaO*t*Bu, Ag_2O, PivOH and related species in this reaction.



Scheme 4.34. Revised mechanistic proposal.

Computational Methods

Calculations were performed by the Lin group at the Hong Kong University of Science and Technology. All calculations were performed using Gaussian 09 D.01 program.[54] The geometries were fully optimised at solvent phase with SMD solvation model[55] (propanoic acid was chosen as solvent because its structure is similar to pivalic acid and the dielectric constants are similar) using M. Head-Gordon's long-range corrected (LC) hybrid density functional ωB97X-D[56] which has been reported to take noncovalent interactions into consideration and worked well for similar systems.[21, 57-58] The effective core potentials (ECPs) of Hay and Wadt with a double-ζ valence basis set (LanL2DZ)[59] were used to describe Pd atom. Polarisation functions were

added for Pd (ζ_f=1.472).[60] The 6-31G(d,p) Pople basis set were used for all other atoms. Frequency calculations were carried out to confirm the characteristics of all of the optimised structures as minima or transition states. Calculations of intrinsic reaction coordinates (IRC)[61] were also performed to confirm that transition states connect two relevant minima. In order to obtain more accurate free energy in solution, further single point calculations were carried out at basis set II level (LanL2DZ(f) for Pd and 6-311++G(d,p) for all other atoms) and solvation effect of propanoic acid was simulated by the SMD continuum solvent model. All natural bond orbital (NBO) analysis were performed using the NBO 3.0 package.[54]

4.5. Conclusions and Future Work

Mechanistic investigations facilitated our understanding of the mechanisms through which 2-coumarins and related heterocycles undergo C–H activation, and subsequently, direct arylation reactions. The majority of the investigations undertaken involved H–D exchange and KIE experiments (both intra- and intermolecular competition experiments). For the three different sets of reaction conditions studied, a concerted metallation-deprotonation was determined to be the most likely mechanism for the C–H activation of these substrates.

The development of a range of protocols to introduce deuterium into the substrates was a necessary, and initially underestimated, challenge of this work.

The understanding of reaction mechanisms is crucial to their future development. For future work on C–H activation reactions, it is proposed that mechanistic investigations should be undertaken shortly after the identification of successful reaction conditions. This could potentially facilitate reaction development and optimisation, prior to the demonstration of the substrate scope.

4.6. References

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Conclusions and Future Work

Conclusions

The arylation of 2-pyrones and related heterocycles has been accomplished through the development of several novel methodologies for the functionalisation of these frameworks. Some of the main results include:

- Regioselective intramolecular cyclisation of the privileged 2-pyrone, 2-pyridone and 2-coumarin motifs under direct arylation conditions was developed.
- For the intramolecular cyclisation at C–3 a broad substrate scope and good to excellent yields were observed.
- The intramolecular cyclisation at C–5 allows the preparation of some previously inaccessible 2-pyrones and 2-pyridones. The reaction proceeds with retention of a C–Cl bond.
- Further elaboration at C–3 of 'cyclised at C–5' 2-pyrones was enabled utilising the retained C–Cl bond in a Suzuki-Miyaura cross-coupling, demonstrating that the C–Cl bond at the C–3 of the 2-pyrone framework is stable enough to withstand the conditions of a direct arylation reaction, but remains reactive enough to participate in Suzuki-Miyaura cross-coupling. This allowed the synthesis of highly decorated 2-pyrone compounds.
- Chlorination of the 2-coumarin and 2-pyrone framework with TCCA, a cheap and environmentally-friendly chlorinating agent, was accomplished.
- A diverse range of aryl and heteroaryl boronic acids, and 2-pyrone, 2-pyridone, 2-coumarin and 2-quinolone frameworks are tolerated by the developed Suzuki-Miyaura conditions in *i*PrOAc, an environmentally benign solvent.

- A practically useful demethylation of the Suzuki-Miyaura products allows access to 3-aryl-4-hydroxy-2-coumarins. This was preferrable to more traditional protecting groups, such as silyl ethers and benzyl groups, which proved difficult to prepare.

- Mechanistic investigations involved H–D exchange and KIE experiments (both intra- and intermolecular competition experiments).

- The development of a range of protocols to introduce deuterium into the substrates was a necessary, and initially underestimated, challenge of this work.

- Based upon these results from different sets of reaction conditions, it was proposed that C–H activation of these substrates occurs *via* concerted-metallation deprotonation.

Future Work

Future work following on from this project will likely involve extension of direct arylation conditions, particularly further development of intermolecular direct arylation and cross-dehydrogenative coupling, to the synthesis of natural products and other biologically active compounds. It is anticipated that extension of mechanistic investigations from the 2-coumarin substrates to more generic biaryls will be pursued.

Chapter 5: Experimental

There are some things you can't share without ending up liking each other, and knocking out a twelve-foot mountain troll is one of them.

J. K. Rowling

Harry Potter and the Philosopher's Stone; 1997

5.1. General Procedures

Solvents and reagents were used as obtained from commercial sources and without purification unless otherwise stated, with the exception of THF, which was freshly distilled from sodium/benzophenone under nitrogen.

Wet flash column chromatography was carried out using Kieselgel silica gel 60, 0.040-0.063 µm (Merck). TLC was carried out on pre-coated silica gel plates (Merck 60 PF254). Visualisation was achieved by UV light.

Microwave reactions were performed in a CEM Discover S-Class Synthesiser with the temperature monitored by infrared temperature control.

Melting points were obtained on a uni-melt Thomas Hoover Capillary melting point apparatus.

IR spectra were recorded on Perkin-Elmer FT-IR Paragon 1000 spectrophotometer. Liquid samples were examined as thin films interspersed on NaCl plates. Solid samples were either dispersed in KBr and recorded as pressed discs, or dissolved in dichloromethane, dispersed as thin films on NaCl plates and the dichloromethane allowed to evaporate before measurement of sample.

NMR spectra were run in $CDCl_3$ using TMS as the internal standard at 25 °C unless otherwise specified. ^{1}H NMR (600 MHz) spectra, ^{1}H NMR (500 MHz) spectra, ^{1}H NMR (400 MHz) spectra and ^{1}H NMR (300 MHz) spectra were recorded on Bruker Avance 600, Bruker Avance 500, Bruker Avance 400 and Bruker Avance 300 NMR spectrometers respectively. ^{13}C (150 MHz) spectra, ^{13}C (126 MHz) spectra, ^{13}C (100 MHz) spectra and ^{13}C (75 MHz) spectra were recorded on Bruker Avance 600, Bruker Avance 500, Bruker Avance 400 and Bruker Avance 300 NMR spectrometers respectively in proton decoupled mode. ^{19}F NMR (282 MHz) spectra were recorded on a Bruker Avance 300 NMR spectrometer in proton decoupled mode. ^{31}P NMR (121 MHz) spectra were recorded on a Bruker Avance 300 NMR spectrometer in proton decoupled mode. All spectra were recorded at University College Cork. Chemical shifts are expressed as parts per million (ppm), relative to TMS

(δH = 0 ppm), the deuterated NMR solvent, usually $CDCl_3$ (δC = 77.0 ppm), H_3PO_4 (δP = 0 ppm) or C_6F_6 (δF = −162.2 ppm). Coupling constants (*J*) are expressed in hertz (Hz). Splitting patterns in ^1H NMR spectra are designated as s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), t (triplet), q (quartet) and m (multiplet). For ^{13}C NMR spectra, the number of attached protons for each signal was determined using the DEPT pulse sequence run in the DEPT-90 and DEPT-135 modes. COSY, HSQC and HMBC experiments were routinely performed to aid the NMR assignment of novel chemical structures.

LRMS were recorded on a Waters Quattro Micro triple quadrupole instrument in ESI mode using 50% acetonitrile-water containing 0.1% formic acid as eluent; samples were made up in acetonitrile or methanol. HRMS were recorded on a Waters LCT Premier Tof LC-MS instrument in ESI mode using 50% acetonitrile-water containing 0.1% formic acid as eluent; samples were made up in acetonitrile or methanol.

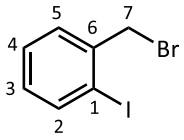
The Microanalysis Laboratory, National University of Ireland, Cork, performed elemental analysis using a Perkin-Elmer 240 and Exeter Analytical CE440 elemental analysers.

5.1.1. Analysis of known and novel compounds

^1H NMR spectra, ^{13}C NMR spectra, LRMS and melting point (if solid) analyses were recorded for all previously prepared compounds. For novel compounds, in addition to the previously mentioned analysis, ^{19}F NMR (where applicable), ^{31}P NMR (where applicable), IR, HRMS and elemental analysis (if possible) were also obtained.

5.2. Synthesis of starting materials

1-(Bromomethyl)-2-iodobenzene (2)[1]

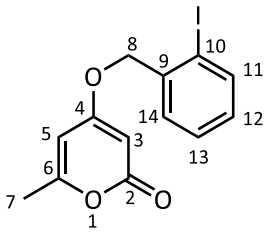


Method 1:[1] PBr_3 (0.2 mL, 2.55 mmol, 0.6 equiv.) was added to a solution of 2-iodobenzyl alcohol **1** (1.0 g, 4.27 mmol, 1.0 equiv.) in distilled THF (5 mL) at 0 °C under nitrogen atmosphere. After 30 min, the reaction was allowed to warm to ambient temperature and the mixture was concentrated under reduced pressure. This crude product was recrystallised from EtOH to give the pure product **2** (0.95 g, 75%) as an off-white solid.

Method 2: To a round-bottomed flask were added 2-iodobenzyl alcohol **1** (4.00 g, 17.09 mmol, 1.0 equiv.), tetrabutylammonium bromide (TBAB) (6.39 g, 19.83 mmol, 1.16 equiv.) and P_2O_5 (5.82 g, 41.0 mmol, 2.4 equiv.). Toluene (70 mL) was added and the reaction mixture was heated to 94 °C and stirred at this temperature for 1.5 h. The reaction mixture was cooled to ambient temperature. The upper organic layer was separated from the residual mass. The residual mass was washed with toluene (2 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 × 30 mL) and brine (1 × 40 mL). The organic extracts were dried, filtered and concentrated under reduced pressure to yield **2** as an off-white solid (4.1 g, 81%); m.p. 54–57 °C (lit.[1] 56–58 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 7.9, 1.2, 1H, C(2)**H**), 7.47 (dd, *J* = 7.7, 1.7, 1H, C(5)**H**), 7.33 (td, *J* = 7.6, 1.2, 1H, C(4)**H**), 6.97 (td, *J* = 7.6, 1.6, 1H, C(3)**H**), 4.59 (s, 2H, C(7)$\mathbf{H}_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2 (q**C**-6), 140.1 (**C**(2)H), 130.5 (**C**(5)H), 130.1 (**C**(3)H), 128.9 (**C**(4)H), 100.0 (q**C**-1), 38.7 (**C**(7)H_2); *m/z* (ES+): 296 ($(M+H)^+$ 6%).

Spectral characteristics were consistent with previously reported data.[1]

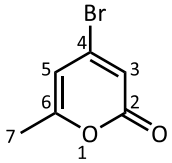
4-((2-Iodobenzyl)oxy)-6-methyl-2*H*-pyran-2-one (4)[2]



To a 3-necked round-bottomed flask were added 4-hydroxy-6-methyl-2*H*-pyran-2-one **3** (0.89 g, 7.02 mmol, 1.0 equiv.), 2-iodobenzyl bromide **2** (2.52 g, 8.42 mmol, 1.2 equiv.), potassium carbonate (2.91 g, 21.05 mmol, 3.0 equiv.) and acetone (30 mL). The resulting reaction mixture was then stirred in an oil bath at 79 °C for 4 h. The reaction mixture was allowed to cool to ambient temperature and filtered. The solid residue was washed with acetone (2 × 20 mL). The acetone portions were combined and concentrated under reduced pressure. The residual mass was dissolved in EtOAc (15 mL) and water (1 × 15 mL). The layers were separated and the aqueous layer was washed with EtOAc (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was purified by recrystallisation from EtOH to yield **4** as a white, crystalline solid (0.882 g, 37%); m.p. 105–106 °C (lit.[2] 101–103 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.8, 1H, C(11)**H**), 7.40 – 7.38 (m, 2H, C(12)**H** & C(14)**H**), 7.10 – 7.05 (m, 1H, C(13)**H**), 5.87 (dd, *J* = 2.0, 0.9, 1H, C(5)**H**), 5.51 (d, *J* = 2.2, 1H, C(3)**H**), 5.01 (s, 2H, C(8)**H**$_2$), 2.23 (s, 3H, C(7)**H**$_3$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9 (q**C**-2), 164.7 (q**C**-6), 162.4 (q**C**-4), 139.7 (**C**(11)H), 136.8 (q**C**-9), 130.3 (**C**(12)H), 129.0 (**C**(14)H), 128.6 (**C**(13)H), 100.3 (**C**(5)H), 97.8 (q**C**-10), 88.8 (**C**(3)H), 74.4 (**C**(8)H$_2$), 19.9 (**C**(7)H$_3$); *m/z* (ES+): 343 ($(M+H)^+$ 100%).

Spectral characteristics were consistent with previously reported data.[2]

4-Bromo-6-methyl-2*H*-pyran-2-one (6)[3]

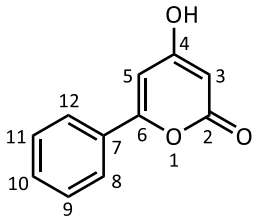


To a 2-necked round-bottomed flask were added 4-hydroxy-6-methyl-*2H*-pyran-2-one **3** (2.0 g, 15.86 mmol, 1.0 equiv.), tetrabutylammonium bromide (TBAB) (5.9 g, 18.40 mmol, 1.16 equiv.), phosphorus pentoxide (5.4 g, 38.10 mmol, 2.4 equiv.) and toluene (50 mL) according to the literature procedure.[4] The resulting reaction mixture was then stirred at 100 °C for 1.5 h. The reaction mixture was allowed to cool to ambient temperature. The clear upper layer was separated from the residual mass. The lower layer was rinsed with toluene (2 × 20 mL). The combined organic extracts were

washed with saturated aqueous $NaHCO_3$ (1 × 30 mL) and brine (1 × 40 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield **6** as an orange solid (1.357 g, 45%) which did not require further purification; m.p. 72–73 °C (lit.[3] 73–74 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.46 (s, 1H, C(3)**H**), 6.21 (s, 1H, C(5)**H**), 2.26 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1 (q**C**-2), 160.7 (q**C**-6), 141.2 (q**C**-4), 114.7 (**C**(5)H), 108.5 (**C**(3)H), 19.8 (**C**(7)H_3); *m/z* (ES+): ^{79}Br 189 ($(M+H)^+$ 28%), ^{81}Br 191 ($(M+H)^+$ 26%).

Spectral characteristics were consistent with previously reported data.[3]

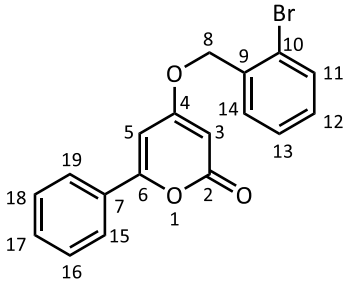
4-Hydroxy-6-phenyl-2*H*-pyran-2-one (8)[2]



A solution of 2,2-dimethyl-6-(2-oxo-2-phenylethyl)-4*H*-1,3-dioxin-4-one **7** (0.25 g, 1.015 mmol, 1.0 equiv.) in toluene (10 mL) was added to a 25 mL round-bottomed flask fitted with stir bar. The solution was heated to 110 °C and stirred at this temperature for 30 min. The reaction mixture was allowed to cool to ambient temperature, and then concentrated under reduced pressure. The resulting crude product was purified by column chromatography (acetone:DCM 50:50) to yield **8** as a pale yellow solid (0.125 g, 65%); m.p. 235–237 °C (lit.[5] 250–251 °C); ^{1}H NMR (300MHz, DMSO-d_6) δ 8.04 – 7.75 (m, 2H, 2 × ArC**H**), 7.53 (dd, *J* = 6.7, 3.6, 3H, 3 × ArC**H**), 6.75 (d, *J* = 2.0, 1H, C(5)**H**), 5.40 (d, *J* = 2.0, 1H, C(3)**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.1 (q**C**-4), 163.5 (q**C**-2), 160.5 (q**C**-6), 131.5 (q**C**-7), 131.4 (**C**(10)H), 129.5 (**C**(9)H & **C**(11)H), 125.9 (**C**(8)H & **C**(12)H), 98.9 (**C**(5)H), 90.1 (**C**(3)H); *m/z* (ES+): 189 ($(M+H)^+$ 50%).

Spectral characteristics were consistent with the previously reported data.[2]

4-((2-Bromobenzyl)oxy)-6-phenyl-2*H*-pyran-2-one (9)[2]

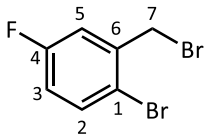


Compound **9** was prepared *via* the procedure described for compound **4** using 4-hydroxy-6-phenyl-*2H*-pyran-2-one **8** (70 mg, 0.345 mmol, 1.0 equiv.) and 2-bromobenzyl bromide (112 mg, 0.414 mmol, 1.2 equiv.). The residue was purified by column chromatography

(MeOH:DCM 0.5:99.5) to yield **9** as a yellow solid (0.0792 g, 64%); m.p. 133–134 °C (lit.[2] 134 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 – 7.78 (m, 2H, 2 × ArC**H**), 7.63 (dd, *J* = 4.0, 1.2, 1H, ArC**H**), 7.51 – 7.42 (m, 4H, 4 × ArC**H**), 7.38 (td, *J* = 7.5, 1.2, 1H, ArC**H**), 7.26 (td, *J* = 7.5, 1.7, 1H, ArC**H**), 6.53 (d, *J* = 2.1, 1H, C(5)**H**), 5.65 (d, *J* = 2.1, 1H, C(3)**H**), 5.17 (s, 2H, C(8)$\mathbf{H}_2$); *m/z* (ES+): ^{79}Br 357 ((M+H)$^+$ 98%), ^{81}Br 359 ((M+H)$^+$ 100%).

Spectral characteristics were consistent with previously reported data.[2]

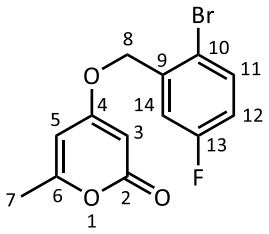
1-Bromo-2-(bromomethyl)-4-fluorobenzene (11)[6]



PBr_3 (0.9 mL, 9.75 mmol, 2.8 equiv.) was added to a solution of (2-bromo-5-fluorophenyl)methanol **10** (1.00 g, 4.88 mmol, 1.0 equiv.) in DCM (40 mL) at ambient temperature and the mixture was stirred overnight. The mixture was then cooled to 0 °C and neutralised with saturated aqueous $NaHCO_3$ (20 mL). The organic component was extracted with DCM (2 × 15 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc:hexanes 30:70) to give **11** as a clear oil (0.465 g, 36%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 8.8, 5.3, 1H, C(2)**H**), 7.20 (dd, *J* = 8.8, 3.0, 1H, C(5)**H**), 6.92 (td, *J* = 8.3, 3.0, 1H, C(3)**H**), 4.55 (s, 2H, C(7)$\mathbf{H}_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9 (d, *J* = 248, q**C**-4), 138.8 (d, *J* = 8, q**C**-6), 134.6 (d, *J* = 8, **C**(2)H), 118.5 (d, *J* = 4, q**C**-1), 118.2 (d, *J* = 24, **C**(3)H), 117.4 (d, *J* = 23, **C**(5)H), 32.5 (d, *J* = 2, **C**(7)H_2).

Spectral characteristics were consistent with previously reported data.[6]

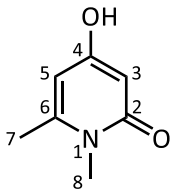
4-((2-Bromo-5-fluorobenzyl)oxy)-6-methyl-2*H*-pyran-2-one (12)[7]



Compound **12** was prepared *via* the procedure described for compound **4** using 4-hydroxy-6-methyl-*2H*-pyran-2-one **3** (0.18 g, 1.43 mmol, 1.0 equiv.) and 1-bromo-2-(bromomethyl)-4-fluorobenzene **11** (0.46 g, 1.72 mmol, 1.2 equiv.). The residue was purified by column chromatography (MeOH:DCM 0.5:99.5) to yield **12** as a white solid (0.209 g, 45%); m.p. 100–102°C (lit.[7] 111–113 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.52 (m, 1H, C(11)**H**), 7.17 (dd, *J* = 9.2, 3.0, 1H, C(12)**H**), 6.97 (td, *J* = 8.4, 3.0, 1H, C(14)**H**), 5.91 (s, 1H, C(5)**H**), 5.49 (d, *J* = 2.2, 1H, C(3)**H**), 5.05 (s, 2H, C(8)**H**$_2$), 2.25 (s, 3H, C(7)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6 (q**C**-4), 164.6 (q**C**-2), 162.7 (q**C**-6), 162.3 (d, *J* = 248, q**C**-13), 136.0 (d, *J* = 8, q**C**-9), 134.2 (d, *J* = 8, **C**(11)H), 117.1 (d, *J* = 23, **C**(12)H), 116.1 (d, *J* = 3, q**C**-10), 115.9 (d, *J* = 25, **C**(14)H), 100.2 (**C**(5)H), 88.8 (**C**(3)H), 69.3 (d, *J* = 1, **C**(8)H_2), 19.9 (**C**(7)H_3); *m/z* (ES-): 311 ($(M-H)^-$ 33%).

Spectral characteristics were consistent with previously reported data.[7]

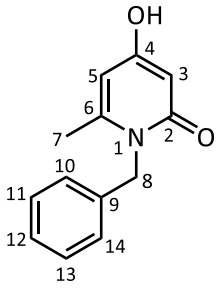
4-Hydroxy-1,6-dimethylpyridin-2(1*H*)-one (13)[8]



To a 250 mL round-bottomed flask were added 4-hydroxy-6-methyl-2-pyrone **3** (1.5 g, 11.89 mmol, 1.0 equiv.), methylamine (1.0 mL, 40% in H_2O, 1.0 equiv.) and deionised water (40 mL). The reaction mixture was stirred for 6 h at 100 °C. The reaction mixture was then cooled to ambient temperature and **13** was isolated by suction filtration as a fine, off-white powder (0.83 g, 50%); m.p. 206–211 °C (lit.[8] 235–236); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.34 (br s, 1H, O–**H**), 5.76 (dd, *J* = 2.7, 0.9, 1H, C(5)**H**), 5.50 (d, *J* = 2.7, 1H, (C(3)**H**), 3.30 (s, 3H, C(8)**H**$_3$), 2.27 (s, 3H, C(7)**H**$_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.9 (q**C**-2), 164.4 (q**C**-4), 148.3 (q**C**-6), 100.0 (**C**(5)H), 96.0 (**C**(3)H), 30.1 (**C**(8)H_3), 20.8 (**C**(7)H_3); *m/z* (ES+): 140 ($(M+H)^+$ 100%).

Spectral characteristic were consistent with previously reported data.[8]

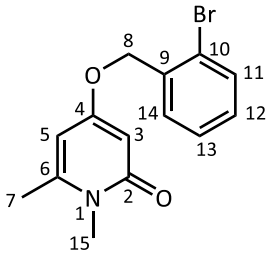
1-Benzyl-4-hydroxy-6-methylpyridin-2(1*H*)-one (14)[9]



Compound **14** was prepared *via* the procedure described for compound **13** using 4-hydroxy-6-methyl-2*H*-pyran-2-one **3** (1.5 g, 11.89 mmol, 1.0 equiv.) and benzylamine (1.3 mL, 11.89 mmol, 1.0 equiv.) to yield **14** as an off-white to grey powder (1.3043 g, 51%) after trituration in EtOH; m.p. 201–207 °C (lit.[9] 205–208 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.51 (br s, 1H, O–**H**), 7.40 – 7.20 (m, 3H, C(11)**H**, C(12)**H** & C(13)**H**), 7.14 – 7.02 (m, 2H, C(10)**H** & C(14)**H**), 5.81 (dd, *J* = 2.7, 0.8, 1H, C(5)**H**), 5.61 (d, *J* = 2.6, 1H, C(3)**H**), 5.20 (s, 2H, C(8)**H**$_2$), 2.17 (s, 3H, C(7)**H**$_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.4 (q**C**-2), 164.5 (q**C**-4), 148.1 (q**C**-9), 138.2 (q**C**-6), 129.0 (**C**(11)H & **C**(13)H), 127.6 (**C**(12)H), 127.3 (**C**(10)H and **C**(14)H), 100.9 (**C**(5)H), 96.3 (**C**(3)H), 45.7 (**C**(9)H_2), 20.4 (**C**(7)H_3); *m/z* (ES-): 214 ($(M-H)^-$ 42%).

Spectral characteristics were consistent with previously reported data.[9]

4-((2-Bromobenzyl)oxy)-1,6-dimethylpyridin-2(1*H*)-one (15)[10]

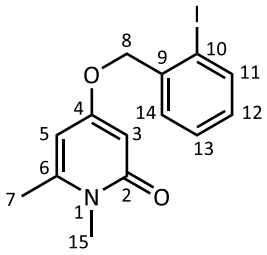


A Schlenk tube was heated under vacuum and refilled with N_2 three times. 4-Hydroxy-1,6-dimethylpyridin-2(1*H*)-one **13** (200 mg, 1.44 mmol, 1.0 equiv.), 2-bromobenzylbromide (402 mg, 1.61 mmol, 1.12 equiv.) and K_2CO_3 (596 mg, 4.31 mmol, 3.0 equiv.) were added. The Schlenk was then evacuated and refilled with N_2 twice. DMF (6 mL) was added to give a cloudy grey suspension. The reaction was stirred overnight under inert atmosphere at ambient temperature. After 18 h, the reaction mixture was diluted with EtOAc (10 mL) and H_2O (10 mL). The organic layer was separated and the aqueous layer washed with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (1 × 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by recrystallisation from DCM/hexanes to give an off-white solid **15** (0.309 g, 70%); m.p. 131–134 °C (lit.[10] 134–135 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58 (dd, *J* = 7.9, 1.2, 1H, C(11)**H**), 7.44 (dd, *J* = 7.6, 1.7, 1H, C(14)**H**), 7.33 (td, *J* = 7.5, 1.2, 1H, C(13)**H**), 7.20 (td, *J* = 7.8, 1.8, 1H, C(12)**H**), 5.92 (d, *J* = 2.8, 1H, C(5)**H**), 5.88 (dd, *J* = 2.9, 0.8, 1H, C(3)**H**), 5.05 (s, 2H, C(8)**H**$_2$), 3.46 (s, 3H, C(15)**H**$_3$), 2.31 (s, 3H, C(7)**H**$_3$); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 165.9 (q**C**-4), 165.3 (q**C**-2), 146.4 (q**C**-6), 134.9 (q**C**-9), 132.8 (**C**(14)H), 129.6 (**C**(12)H), 128.9 (**C**(11)H), 127.6 (**C**(13)H), 122.6 (q**C**-10), 100.8 (**C**(5)H), 95.8 (**C**(3)H), 69.2 (**C**(8)H_2), 30.6 (**C**(15)H_3), 20.9 (**C**(7)H_3); *m/z* (ES+): 310 (^{81}Br (M+H)$^+$ 52%).

Spectral characteristics were consistent with previously reported data.[10]

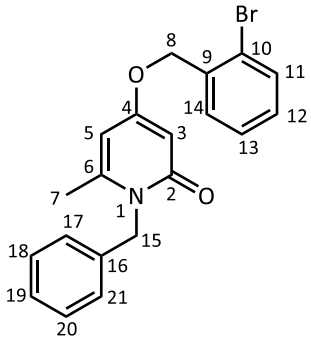
4-((2-Iodobenzyl)oxy)-1,6-dimethylpyridin-2(1*H*)-one (16)



Method 1: Compound **16** was prepared *via* the procedure described for compound **15** using 4-hydroxy-1,6-dimethylpyridin-2(1*H*)-one **13** (150 mg, 1.08 mmol, 1.0 equiv.), 2-iodobenzylbromide **2** (358 mg, 1.21 mmol, 1.12 equiv.) and Na_2CO_3 (447 mg, 4.22 mmol, 3.9 equiv.). The residue was purified by column chromatography (EtOAc:hexanes 50:50) to give **16** as an off-white solid (0.112 g, 29%).

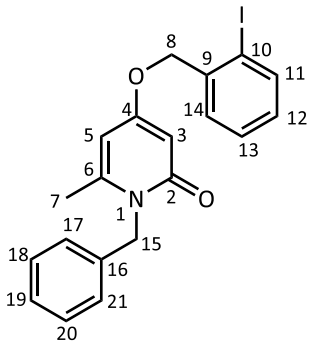
Method 2: Compound **16** was prepared *via* the procedure described for compound **4** using 4-hydroxy-1,6-dimethylpyridin-2(1*H*)-one **13** (0.5 g, 3.59 mmol, 1.0 equiv.) and 2-iodobenzylbromide **2** (1.3 g, 4.31 mmol, 1.2 equiv.). The residue was purified by column chromatography (EtOAc:hexanes 80:20) to give **16** as a white solid (0.634 g, 50%); m.p. 134–136 °C; IR ν_{max} (KBr) 1644 (amide C=O stretch), 1591 (aromatic C–C stretch), 1356 (ether C–O stretch), 1200 (amide C–N stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.9, 1H, C(11)**H**), 7.44 – 7.31 (m, 2H, C(13)**H** & C(14)**H**), 7.03 (td, *J* = 7.5, 1.8, 1H, C(12)**H**), 5.93 (d, *J* = 2.6, 1H, C(3)**H**), 5.88 (d, *J* = 2.4, 1H, C(5)**H**), 4.96 (s, 2H, C(8)$\mathbf{H}_2$), 3.47 (s, 3H, C(15)$\mathbf{H}_3$), 2.31 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9 (q**C**-4), 165.3 (q**C**-2), 146.4 (q**C**-6), 139.5 (**C**(14)H), 137.8 (q**C**-9), 129.8 (**C**(12)H), 128.7 (**C**(11)H), 128.4 (**C**(13)H), 100.8 (**C**(5)H), 97.5 (q**C**-10), 95.9 (**C**(3)H), 73.7 (**C**(8)H_2), 30.6 (**C**(15)H_3), 20.9 (**C**(7)H_3); *m/z* (ES+): 356 ((M+H)$^+$ 18%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{14}H_{15}INO_2$ 356.0147; Found 356.0144.

1-Benzyl-4-((2-bromobenzyl)oxy)-6-methylpyridin-2(1*H*)-one (17)[2]



Compound **17** was prepared *via* the procedure described for compound **15** using 1-benzyl-4-hydroxy-6-methylpyridin-2(1*H*)-one **14** (300 mg, 1.39 mmol, 1.0 equiv.) and 2-bromobenzylbromide **2** (390 mg, 1.56 mmol, 1.12 equiv.). The residue was purified by column chromatography (EtOAc:hexanes 50:50) to give an off-white solid **17** (0.282 g, 53%); m.p. 115–118 °C (lit.[2] 116–117 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.9, 1.2, 1H, C(11)**H**), 7.47 (dd, *J* = 7.8, 1.6, 1H, C(14)**H**), 7.39 – 7.11 (m, 7H, 7 × ArC**H**), 6.20 (d, *J* = 2.7, 1H, C(3)**H**), 5.95 (dd, *J* = 3.0, 0.7, 1H, C(5)**H**), 5.30 (s, 2H, C(8)$\mathbf{H}_2$), 5.10 (s, 2H, C(15)$\mathbf{H}_2$), 2.25 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5 (q**C**-4), 165.2 (q**C**-2), 147.0 (q**C**-6), 136.4 (q**C**-9), 134.7 (q**C**-16), 132.9 (**C**(14)H), 129.9 (**C**(12)H), 129.3 (**C**(11)H), 128.8 (**C**(18)H & **C**(20)H), 127.7 (**C**(13)H), 127.4 (**C**(17)H & **C**(21)H), 126.4 (**C**(19)H), 122.9 (q**C**-10), 102.2 (**C**(5)H), 95.9 (**C**(3)H), 69.7 (**C**(8)H_2), 46.9 (**C**(15)H_2), 20.5 (**C**(7)H_3); *m/z* (ES+): 385 (^{79}Br (M+H)$^+$ 86%).

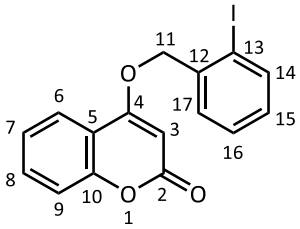
1-Benzyl-4-((2-iodobenzyl)oxy)-6-methylpyridin-2(1*H*)-one (18)



Compound **18** was prepared *via* the procedure described for compound **16** using 1-benzyl-4-hydroxy-6-methylpyridin-2(1*H*)-one **14** (200 mg, 0.93 mmol, 1.0 equiv.) and 2-iodobenzylbromide **2** (309 mg, 1.04 mmol, 1.12 equiv.). The residue was purified by column chromatography (EtOAc:hexanes 50:50) to give an off-white solid **18** (0.221 g, 55%); m.p. 129–134 °C; IR ν_{max} (KBr) 1653 (amide C=O stretch), 1591 (aromatic C–C stretch), 1242 (amide C–N stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.9, 0.7, 1H, C(11)**H**), 7.47 – 7.10 (m, 7H, 7 × ArC**H**), 7.04 (td, 1H, *J* = 7.6, 1.8, C(12)**H**), 6.01 (d, *J* = 2.7, 1H, C(5)**H**), 5.88 (d, *J* = 2.3, 1H, C(3)**H**), 5.29 (s, 2H, C(8)$\mathbf{H}_2$), 5.00 (s, 2H, C(15)$\mathbf{H}_2$), 2.23 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2 (q**C**-4), 165.3 (q**C**-2), 146.7 (q**C**-6), 139.5 (**C**(14)H), 137.8 (q**C**-9), 136.8 (q**C**-16), 129.9 (**C**(12)H), 128.8 (**C**(18)H, **C**(19)H & **C**(20)H), 128.4 (**C**(11)H), 127.3 (**C**(13)H), 126.4 (**C**(17)H & **C**(21)H), 101.4 (**C**(5)H), 97.5 (q**C**-10), 96.1 (**C**(3)H), 73.8 (**C**(8)H_2), 46.6

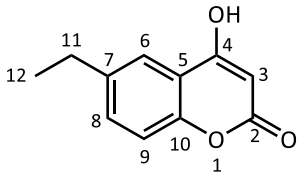
(**C**(15)H_2), 20.6 (**C**(7)H_3); *m/z* (ES+): 432 ((M+H)$^+$ 28%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{20}H_{19}INO_2$ 432.0460; Found 432.0444.

4-((2-Iodobenzyl)oxy)-*2H*-chromen-2-one (20)



Compound **20** was prepared *via* the procedure described for compound **4** using 4-hydroxy-2*H*-chromen-2-one **19** (1.00 g, 6.17 mmol, 1.0 equiv.) and 2-iodobenzyl bromide **2** (2.20 g, 7.40 mmol, 1.2 equiv.). The residue was purified by column chromatography (DCM) to give **20** as a white solid (1.0521 g, 45%); m.p. 159–162 °C; IR ν_{max} (KBr) 1717 (ester C=O stretch), 1624 (alkene C=C stretch), 1566 (aromatic C–C stretch), 1250 (ester C–O stretch), 1189 (ether C–O stretch), 935 (alkene C–H bend), 750 (C–I stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 7.9, 1.1, 1H, C(14)**H**), 7.89 (dd, *J* = 7.9, 1.6, 1H, C(17)**H**), 7.61 – 7.53 (m, 1H, C(16)**H**), 7.52 – 7.39 (m, 2H, C(6)**H** & C(8)**H**), 7.37 – 7.28 (m, 2H, C(7)**H** & C(9)**H**), 7.11 (td, *J* = 7.5, 1.9, 1H, C(15)**H**), 5.81 (s, 1H, C(3)**H**), 5.21 (s, 2H, C(8)$\mathbf{H}_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1 (q**C**-4), 162.7 (q**C**-2), 153.4 (q**C**-10), 139.8 (**C**(14)H), 136.7 (q**C**-12), 132.5 (**C**(15)H), 130.5 (**C**(17)H), 129.1 (**C**(8)H), 128.6 (**C**(16)H), 124.0 (**C**(7)H), 123.2 (**C**(6)H), 116.9 (**C**(9)H), 115.6 (q**C**-5), 97.9 (q**C**-13), 91.6 (**C**(3)H), 74.8 (**C**(11)H_2); *m/z* (ES-): 377 ((M-H)$^-$ 8%); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{16}H_{12}O_3I$ 378.9831; Found 378.9850.

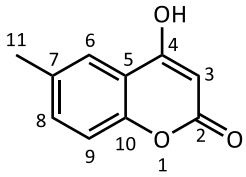
6-Ethyl-4-hydroxy-2*H*-chromen-2-one (21)[11]



Following the literature procedure,[12] a mixture of 4-ethylphenol (1.00 g, 8.02 mmol, 1.0 equiv.) and Meldrum's acid (1.18 g, 8.02 mmol, 1.0 equiv.) was stirred at 100 °C for 3 h. The small remaining amount of acetone was removed by vacuum. Eaton's reagent (24.1 mL, 127 mmol, 16 equiv.) was added to the mixture and was stirred at 70 °C for 4 h. Water (25 mL) was then added to this mixture while stirring vigorously. The precipitate was filtered by suction, washed with water and dried. This solid was then purified by recrystallisation from EtOH to give **21** as a brown crystalline solid (1.1612 g, 76%); m.p. 217–219 °C (lit.[11] 216–218 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.44 (br s, 1H, O–**H**), 7.63 (d, *J* = 2.1, C(6)**H**), 7.48 (dd, *J* = 8.5, 2.2, C(8)**H**), 7.28 (d, *J* = 8.4, 1H, C(9)**H**), 5.58 (s, 1H, C(3)**H**), 2.68 (q, *J* = 7.5,

2H, C(11)**H**$_2$), 1.20 (t, *J* = 7.6, 3H, C(12)**H**$_3$); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ 166.1 (q**C**-4), 162.5 (q**C**-2), 152.3 (q**C**-10), 139.9 (q**C**-7), 132.9 (**C**(8)H), 122.0 (**C**(6)H), 116.7 (**C**(9)H), 116.0 (q**C**-5), 91.4 (**C**(3)H), 27.9 (**C**(11)H$_2$), 16.0 (**C**(12)H$_3$); *m/z* (ES+): 191 ((M+H)$^+$ 90%).

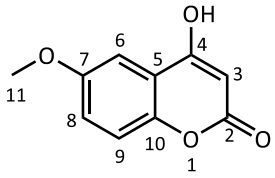
4-Hydroxy-6-methyl-*2H*-chromen-2-one (22)[12]



Compound **22** was prepared *via* the procedure described for compound **21** using 4-methylphenol (1.00 g, 9.25 mmol, 1.0 equiv.) to yield **22** as a brown crystalline solid (1.1636 g, 71%); m.p. 246–252 °C (lit.[12] 261.0–261.2 °C); ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 12.50 (br s, 1H, O–**H**), 7.62 (s, 1H, C(6)**H**), 7.46 (dd, *J* = 8.4, 2.1, 1H, C(8)**H**), 7.27 (d, *J* = 8.4, 1H, C(9)**H**), 5.57 (s, 1H, C(3)**H**), 2.38 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ 166.1 (q**C**-4), 162.5 (q**C**-2), 152.1 (q**C**-10), 133.9 (q**C**-7), 133.6 (**C**(8)H), 123.2 (**C**(6)H), 116.6 (**C**(9)H), 116.0 (q**C**-5), 91.4 (**C**(3)H), 20.8 (**C**(11)H$_3$); *m/z* (ES+): 177.3 ((M+H)$^+$ 100%).

Spectral characteristics were consistent with previously reported data.[12]

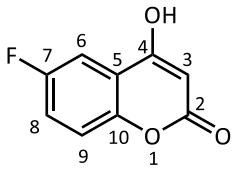
4-Hydroxy-6-methoxy-*2H*-chromen-2-one (23)[12]



Compound **23** was prepared *via* the procedure described for compound **21** using 4-methyloxyphenol (0.67 g, 5.40 mmol, 1.0 equiv.) to yield **23** as a brown crystalline solid (0.32 g, 31%); m.p. >250 °C (lit.[12] 254.4–254.7 °C); ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 12.51 (br s, 1H, O–**H**), 7.36 – 7.29 (m, 1H, C(9)**H**), 7.27 – 7.20 (m, 2H, C(6)**H** & C(8)**H**), 5.60 (s, 1H, C(3)**H**), 3.82 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ 165.8 (q**C**-4), 162.5 (q**C**-2), 155.8 (q**C**-7), 148.3 (q**C**-10), 120.9 (**C**(9)H), 118.1 (**C**(8)H), 116.7 (q**C**-5), 105.5 (**C**(6)H), 91.7 (**C**(3)H), 56.1 (**C**(11)H$_3$); *m/z* (ES+): 193 ((M+H)$^+$ 100%).

Spectral characteristics were consistent with previously reported data.[13]

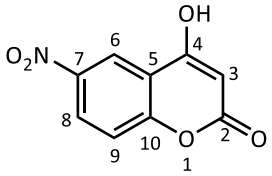
6-Fluoro-4-hydroxy-2*H*-chromen-2-one (24)[14]



A 50 mL 2-neck round-bottomed flask was heated under vacuum and refilled with N_2 three times. NaH (2.4 g, 55% in oil, 54.5 mmol, 8.4 equiv.) was added. The flask was evacuated and refilled with N_2 three times. The flask was cooled to 0 °C, then diethyl carbonate (2 mL) was added and the suspension stirred. A solution of 5-fluoro-2-hydroxy-acetophenone (1.0 g, 6.49 mmol, 1.0 equiv.) in diethyl carbonate (2 mL) was added to the NaH suspension over 10 min at 0 °C. The resulting mixture was allowed to warm to ambient temperature, 20 mL toluene was added. The mixture heated to 110 °C and stirred overnight. The mixture was cooled and filtered to obtain a yellow solid. The solid was added to ice-cold H_2O (20 mL) in a 250 mL beaker and stirred with a spatula until hydrogen gas evolution ceased. The cloudy yellow solution was acidified using 2 M aqueous HCl (approx. 25 mL) until precipitation appeared to cease. The precipitate was isolated by filtration, dissolved in EtOAc and the organic layer concentrated under reduced pressure to afford an off-white solid **24** (0.2995 g, 26%); m.p. 243–245 °C (lit.[13] 240–241 °C); IR ν_{max} (film) 1699 (ester C=O stretch), 1618 (C=C stretch), 1573 (aromatic C–C stretch), 1224 (C–O stretch), 812 (C–F stretch); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.59 – 7.38 (m, 3H, 3 × ArC**H**), 5.56 (s, 1H, C(3)**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.0 (q**C**-4), 162.7 (q**C**-2), 158.3 (d, *J* = 240, q**C**-7), 150.4 (d, *J* = 2, q**C**-10), 120.0 (d, *J* = 25, **C**(8)H), 118.8 (d, *J* = 8, q**C**-5 & **C**(9)H), 109.3 (d, *J* = 25, **C**(6)H), 91.12 (**C**(3)H); ^{19}F NMR (282 MHz, DMSO-d_6) δ: -118 (s, C(7)**F**); *m/z* (ES-): 179 ($(M-H)^-$ 100%).

Spectral characteristics were consistent with previously reported data.[14]

4-Hydroxy-6-nitro-*2H*-chromen-2-one (25)[15]

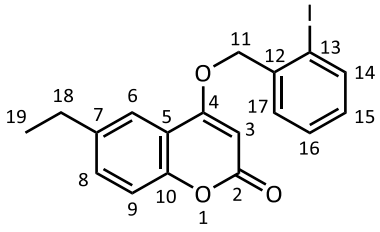


Modifying a literature procedure,[15] a 100 mL round-bottomed flask fitted with stir bar was placed in an ice bath. 96% aqueous H_2SO_4 (20 mL) was added and stirred for 5 min until cool, then 65% aqueous HNO_3 (0.43 mL, 1.0 equiv.) was added and the mixture was stirred for 5 min. 4-Hydroxycoumarin **19** (1.0 g, 1.0 equiv.) was slowly added to the stirring solution to ensure dissolution. The reaction was

maintained at 0 °C for 1 h. The mixture was then poured onto ice water (100 mL) and stirred. A yellow precipitate formed, which was isolated by suction filtration. The crude product was purified by recrystallisation from EtOH to give **25** as a pale yellow solid (0.329 g, 26%); m.p. >250 °C (lit.[15] 253–254 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (1H, d, *J* = 2.8, C(6)**H**), 8.46 (dd, *J* = 9.2, 2.8, 1H, C(8)**H**), 7.62 (d, *J* = 9.2, 1H, C(9)**H**), 5.72 (s, 1H, C(3)**H**); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5 (q**C**-4), 160.8 (q**C**-2), 157.1 (q**C**-10), 143.2 (q**C**-7), 127.3 (**C**(8)H), 119.1 (**C**(6)H), 118.1 (**C**(9)H), 116.4 (q**C**-5), 92.0 (**C**(3)H); *m/z* (ES+): 208 ($(M+H)^+$ 6%) 163 ($(M-NO_2)^+$ 100%).

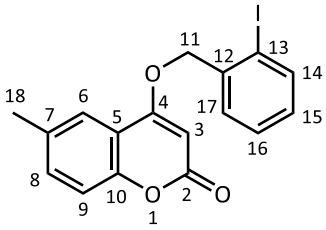
Spectral characteristics were consistent with previously reported data.[15]

6-Ethyl-4-((2-iodobenzyl)oxy)-*2H*-chromen-2-one (26)



Compound **26** was prepared *via* the procedure described for compound **4** using 6-ethyl-4-hydroxy-2*H*-chromen-2-one **21** (0.5 g, 2.63 mmol, 1.0 equiv.) and 2-iodobenzyl bromide **2** (0.94 g, 3.15 mmol, 1.2 equiv.). The residue was purified by column chromatography (DCM) to give **26** as a pale yellow solid (0.450 g, 42%); m.p. 156–161 °C; IR ν_{max} (KBr) 1716 (ester C=O stretch), 1632 (alkene C=C stretch), 1578 (aromatic C–C stretch), 1366 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.3, 1H, C(14)**H**), 7.67 (d, *J* = 2.0, 1H, C(6)**H**), 7.54 – 7.35 (m, 3H, C(8)**H**, C(9)**H**, C(16)**H**), 7.30 – 7.21 (m, 1H, C(17)**H**), 7.11 (td, *J* = 7.6, 1.7, 1H, C(15)**H**), 5.77 (s, 1H, C(3)**H**), 5.19 (s, 2H, C(11)$\mathbf{H}_2$), 2.71 (q, *J* = 7.5, 2H, C(18)$\mathbf{H}_2$), 1.26 (t, *J* = 7.6, 3H, C(19)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1 (q**C**-4), 162.9 (q**C**-2), 151.7 (q**C**-10), 140.2 (q**C**-12), 139.8 (**C**(14)H), 136.8 (q**C**-7), 132.4 (**C**(15)H), 130.5 (**C**(17)H), 129.1 (**C**(8)H), 128.6 (**C**(16)H), 121.7 (**C**(6)H), 116.7 (**C**(9)H), 115.3 (q**C**-5), 97.9 (q**C**-13), 91.5 (**C**(3)H), 74.8 (**C**(11)H_2), 28.4 (**C**(18)H_2), 15.8 (**C**(19)H_3); *m/z* (ES+): 407 ($(M+H)^+$ 18%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{16}O_3I$ 407.0144; Found 407.0146; Anal. Calcd for $C_{18}H_{15}O_3I$: C, 53.22; H, 3.72. Found: C, 53.11; H, 3.69.

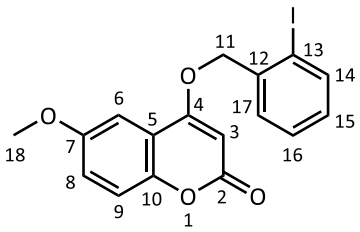
4-((2-Iodobenzyl)oxy)-6-methyl-*2H*-chromen-2-one (27)[7]



Compound **27** was prepared *via* the procedure described for compound **4** using 4-hydroxy-6-methyl-2*H*-chromen-2-one **22** (0.50 g, 2.84 mmol, 1.0 equiv.) and 2-iodobenzyl bromide **2** (1.01 g, 3.41 mmol, 1.2 equiv.). The residue was purified by column chromatography (DCM) to give **27** as a pale yellow solid (0.467 g, 42%); m.p. 171–173 °C (lit.[7] 168–169 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.9, 1H, C(14)**H**), 7.64 (d, *J* = 1.4, 1H, C(6)**H**), 7.54 – 7.32 (m, 3H, C(8)**H**, C(9)**H**, C(16)**H**), 7.25 – 7.18 (m, 1H, C(17)**H**), 7.11 (td, *J* = 7.6, 1.8, 1H, C(15)**H**), 5.77 (s, 1H, C(3)**H**), 5.18 (s, 2H, C(11)$\mathbf{H}_2$), 2.41 (s, 3H, C(18)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1 (q**C**-4), 162.9 (q**C**-2), 151.6 (q**C**-10), 139.8 (**C**(14)H), 136.8 (q**C**-12), 133.8 (q**C**-7), 133.6 (**C**(8)H), 130.5 (**C**(15)H), 129.1 (**C**(17)H), 128.7 (**C**(16)H), 122.8 (**C**(6)H), 116.6 (**C**(9)H), 115.2 (q**C**-5), 97.9 (q**C**-13), 91.5 (**C**(3)H), 74.8 (**C**(11)H_2), 20.9 (**C**(18)H_3); *m/z* (ES+): 393 ($(M+H)^+$ 34%).

Spectral characteristics were consistent with previously reported data.[7]

4-((2-Iodobenzyl)oxy)-6-methoxy-*2H*-chromen-2-one (28)[7]

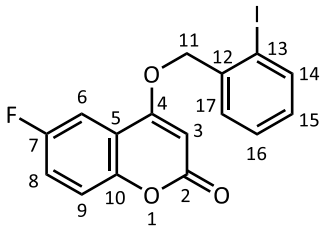


A solution of 4-hydroxy-6-methoxy-2*H*-chromen-2-one **23** (100 mg, 0.52 mmol, 1.0 equiv.), 2-iodobenzyl bromide **2** (309 mg, 1.04 mmol, 2.0 equiv.) and CsF (158 mg, 1.04 mmol, 2.0 equiv.) in DMF (3 mL) was stirred at ambient temperature for 24 h.[16] H_2O (10 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with H_2O (2 × 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (MeOH:DCM 1:99) to give **28** as a white solid (0.0424 g, 20%); m.p. 149–151 °C (lit.[7] 132–133 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 7.9, 0.9, 1H, ArC**H**), 7.51 – 7.37 (m, 2H, 2 × ArC**H**), 7.34 – 7.27 (m, 1H, ArC**H**), 7.26 (d, *J* = 0.6, 1H, ArC**H**), 7.18 – 7.07 (m, 2H, 2 × ArC**H**), 5.79 (s, 1H, C(3)**H**), 5.21 (s, 2H, C(11)$\mathbf{H}_2$), 3.85 (s, 3H, C(18)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8 (q**C**-4), 162.9 (q**C**-2), 155.9 (q**C**-7), 147.9 (q**C**-10), 139.9 (**C**(14)H), 136.7 (q**C**-12), 130.5 (**C**(15)H), 129.2 (**C**(17)H), 128.6 (**C**(16)H), 120.2 (**C**(9)H), 117.9 (**C**(8)H), 115.9 (q**C**-5), 105.5

(**C**(6)H), 97.9 (q**C**-13), 91.9 (**C**(3)H), 74.8 (**C**(11)H_2), 55.9 (**C**(18)H_3); *m/z* (ES+): 409 ($(M+H)^+$ 100%).

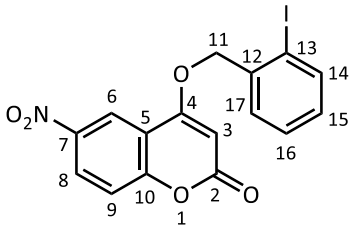
Spectral characteristics were consistent with previously reported data.[7]

6-Fluoro-4-(2-iodo(benzyloxy))-*2H*-chromen-2-one (29)



Compound **29** was prepared *via* the procedure described for compound **4** using 6-fluoro-4-hydroxy-2*H*-chromen-2-one **24** (0.25 g, 1.388 mmol, 1.0 equiv.) and 2-iodobenzyl bromide **2** (0.50 g, 1.665 mmol, 1.2 equiv.). The residue was purified by column chromatography (MeOH:DCM 0.5:99.5) to give **29** as a white solid (0.283 g, 52%); m.p. 157–159 °C; IR ν_{max} (film) 1720 (C=O stretch), 1576 (C=C stretch), 1179 (C–O stretch), 826 (C–F stretch), 749 (C–I stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 – 7.88 (m, 1H, C(14)**H**), 7.54 (dd, *J* = 8.3, 2.5, 1H, C(6)**H**), 7.39 – 7.51 (m, 2H, C(8)**H** & C(9)**H**), 7.36 – 7.23 (m, 2H, C(16)**H** & C(17)**H**), 7.17 – 7.08 (m, 1H, C(15)**H**), 5.85 (s, 1H, C(3)**H**), 5.20 (s, 2H, C(11)$\mathbf{H}_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2 (d, *J* = 3, q**C**-4), 162.4 (q**C**-2), 158.7 (d, *J* = 244, q**C**-7), 149.5 (d, *J* = 2, q**C**-10), 139.9 (**C**(14)H), 136.4 (q**C**-12), 130.7 (**C**(15)H), 129.3 (**C**(17)H), 128.7 (**C**(16)H), 120.1 (d, *J* = 25, **C**(8)H), 118.5 (d, *J* = 8, **C**(9)H), 116.5 (d, *J* = 9, q**C**-5), 109.1 (d, *J* = 25, **C**(6)H), 98.1 (q**C**-13), 92.3 (**C**(3)H), 75.0 (**C**$(11)_2$); ^{19}F NMR (282 MHz, $CDCl_3$) δ -117 (s, C(7)**F**); *m/z* (ES+): 397 ($[M+H]^+$ 54%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{11}O_3FI$ 396.9737; Found 396.9733.

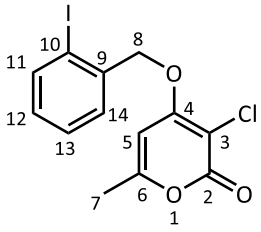
4-((2-Iodobenzyl)oxy)-6-nitro-*2H*-chromen-2-one (30)



Compound **30** was prepared *via* the procedure described for compound **28** using 4-hydroxy-6-nitro-2*H*-chromen-2-one **25** (100 mg, 0.48 mmol, 1.0 equiv.) and 2-iodobenzyl bromide **2** (287 mg, 0.97 mmol, 2.0 equiv.). The residue was purified by column chromatography (DCM) to give **30** as a white solid (0.102 g, 50%); m.p. 182–184 °C; IR ν_{max} (film) 1728 (C=O stretch), 1626 (C=C stretch), 1531 (N–O asymmetric stretch), 1338 (N–O symmetric stretch); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (1H, d, *J* = 2.7, C(6)**H**), 8.43 (dd, *J* = 9.1, 2.7, 1H, C(8)**H**),

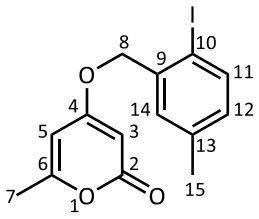
7.96 (d, *J* = 8.0, 1H, C(14)**H**), 7.53 – 7.42 (m, 3H, C(9)**H**, C(16)**H** & C(17)**H**), 7.20 – 7.13 (m, 1H, C(15)**H**), 5.91 (s, 1H, C(3)**H**), 5.27 (s, 2H, C(11)$\mathbf{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7 (q**C**-4), 160.9 (q**C**-2), 156.8 (q**C**-10), 144.0 (q**C**-7), 140.1 (**C**(14)H), 135.9 (q**C**-12), 131.0 (**C**(15)H), 129.5 (**C**(17)H), 128.9 (**C**(16)H), 127.3 (**C**(8)H), 119.9 (**C**(6)H), 118.1 (**C**(9)H), 116.1 (q**C**-5), 98.3 (q**C**-13), 92.9 (**C**(3)H), 75.5 (**C**(11)H_2); *m/z* (ES+): 424 ($(M+H)^+$ 98%); Anal. Calcd for $C_{16}H_{10}O_5IN$: C, 45.41; H, 2.38; N, 3.31. Found: C, 45.76; H, 2.64; N, 2.89.

3-Chloro-4-((2-iodobenzyl)oxy)-6-methyl-2*H*-pyran-2-one (47)



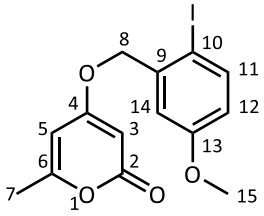
To a stirring solution of 4-((2-iodobenzyl)oxy)-6-methyl-2*H*-pyran-2-one **4** (0.54 g, 1.578 mmol, 1.0 equiv.) in $CHCl_3$ (8 mL) in a 25 mL round-bottomed flask were added *N*-chlorosuccinimide (NCS) (0.25 g, 1.894 mmol, 1.2 equiv.) and trifluoroacetic acid (TFA) (0.15 mL, 1.894 mmol, 1.2 equiv.). The flask was covered in aluminium foil and placed in an oil bath preheated to 55 °C. The resulting reaction mixture was then stirred at 55 °C for 18 h. The reaction mixture was allowed to cool to ambient temperature. The mixture was diluted with $CHCl_3$ (10 mL) and washed with saturated aqueous $NaHCO_3$ (1 × 15 mL) and H_2O (2 × 15 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (DCM) to yield **47** as a white solid (0.387 g, 65%); m.p. 183–185 °C; IR ν_{max} (film) 1725 (C=O stretch), 1639 (alkene C=C stretch), 1542 (aromatic C-C stretch), 1322 (C-O stretch), 758 (C–X stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.0, 1.0, 1H, ArC**H**), 7.53 – 7.38 (m, 2H, 2 × ArC**H**), 7.09 (td, *J* = 7.5, 1.9, 1H, ArC**H**), 6.06 (d, *J* =0.8, 1H, C(5)**H**), 5.21 (s, 2H, C(8)$\mathbf{H}_2$), 2.29 (d, *J* = 0.8, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0 (q**C**-4), 161.8 (q**C**-2), 160.8 (q**C**-6), 139.5 (Ar**C**H), 136.7 (q**C**-9), 130.3 (Ar**C**H), 128.9 (Ar**C**H), 128.4 (Ar**C**H), 100.5 (q**C**-3), 96.4 (q**C**-10), 96.1 (**C**(5)H), 75.3 (**C**(8)H_2), 20.3 (**C**(7)H_3); *m/z* (ES+): 377 ($(M+H)^+$ 20%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{11}O_3ICl$ 376.9441; Found 376.9446.

4-((2-Iodo-5-methylbenzyl)oxy)-6-methyl-2*H*-pyran-2-one (48)



Compound **48** was prepared *via* the procedure described for compound **4** using 4-hydroxy-6-methyl-2*H*-pyran-2-one **3** (220 mg, 1.742 mmol, 1.0 equiv.) and 2-iodo-5-methylbenzylbromide (650 mg, 2.090 mmol, 1.2 equiv.). The residue was purified by column chromatography (MeOH:DCM 0.5:99.5) to yield **48** as a white solid (0.236 g, 38%); m.p. 125–127 °C; IR ν_{max} (film) 1719 (ester C=O stretch), 1649 (alkene C=C stretch), 1566 (aromatic C-C stretch), 1245 (ester C-O stretch), 1013 (ether C-O stretch), 806 (alkene C-H bend); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0, 1H, C(11)**H**), 7.20 (d, *J* = 1.6, 1H, C(14)**H**), 6.89 (dd, *J* = 8.0, 1.7, 1H, C(12)**H**), 5.88 (dd, *J* = 2.1, 0.9, 1H, C(5)**H**), 5.50 (d, *J* = 2.1, 1H, C(3)**H**), 4.96 (s, 2H, C(8)**H**$_2$), 2.32 (s, 3H, C(15)**H**$_3$), 2.22 (s, 3H, C(7)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0 (q**C**-4), 164.8 (q**C**-2), 162.4 (q**C**-6), 139.4 (**C**(11)H), 138.7 (q**C**-9), 136.4 (q**C**-13), 131.3 (**C**(14)H), 130.0 (**C**(12)H), 100.4 (**C**(5)H), 93.7 (q**C**-10), 88.7 (**C**(3)H), 74.4 (**C**(8)H_2), 21.0 (**C**(15)H_3), 19.9 (**C**(7)H_3); *m/z* (ES+): 357 ($(M+H)^+$ 40%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{14}IO_3$ 356.9988; Found 356.9987.

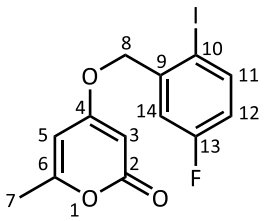
4-((2-Iodo-5-methoxybenzyl)oxy)-6-methyl-2*H*-pyran-2-one (49)



Compound **49** was prepared *via* the procedure described for compound **4** using 4-hydroxy-6-methyl-2*H*-pyran-2-one **3** (138 mg, 1.096 mmol, 1.0 equiv.) and 2-iodo-5-methoxybenzylbromide (430 mg, 1.315 mmol, 1.2 equiv.). The residue was purified by column chromatography (MeOH:DCM 0.5:99.5) to yield **49** as a yellow solid (0.015 g, 4%), with the remainder (0.197 g) isolated as an inseparable mixture which was used without further purification in the next step; m.p. 100–104 °C; IR ν_{max} (film) 1727 (ester C=O stretch), 1651 (alkene C=C stretch), 1566 (aromatic C-C stretch), 1244 (ester C-O stretch), 1000 (ether C-O stretch), 811 (alkene C-H bend); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.7, 1H, C(11)**H**), 6.96 (d, *J* = 3.0, 1H, C(14)**H**), 6.66 (dd, *J* = 8.7, 3.0, 1H, C(12)**H**), 5.88 (dd, *J* = 2.1, 0.9, 1H, C(5)**H**), 5.49 (d, *J* = 2.1, 1H, C(3)**H**), 4.96 (s, 2H, C(8)**H**$_2$), 3.80 (s, 3H, C(15)**H**$_3$), 2.23 (s, 3H, C(7)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9 (q**C**-4), 164.7 (q**C**-2), 162.4 (q**C**-6), 160.2

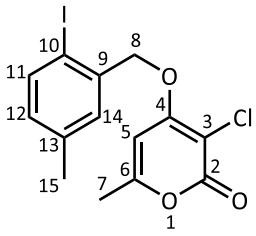
(q**C**-13), 140.1 (**C**(11)H), 137.7 (q**C**-9), 115.8 (**C**(12)H), 115.3 (**C**(14)H), 100.3 (**C**(5)H), 88.9 (**C**(3)H), 85.6 (q**C**-10), 74.2 (**C**(8)H_2), 55.5 (**C**(15)H_3), 19.9 (**C**(7)H_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{14}IO_4$ 372.9937; Found 372.9949.

4-((5-Fluoro-2-iodobenzyl)oxy)-6-methyl-2*H*-pyran-2-one (50)



Compound **50** was prepared *via* the procedure described for compound **4** using 4-hydroxy-6-methyl-2*H*-pyran-2-one **3** (125 mg, 0.992 mmol, 1.0 equiv.) and 5-fluoro-2-iodobenzylbromide (375 mg, 1.191 mmol, 1.2 equiv.). The residue was purified by column chromatography (DCM) to yield **50** as a pale yellow solid (0.143 g, 40%); m.p. 123–126 °C; IR ν_{max} (film) 1714 (ester C=O stretch), 1650 (alkene C=C stretch), 1569 (aromatic C-C stretch), 1239 (ester C-O stretch), 1020 (ether C-O stretch), 666 (alkene C-H bend); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.7, 5.5, 1H, C(11)**H**), 7.15 (dd, *J* = 9.3, 3.0, 1H, C(14)**H**), 6.84 (td, *J* = 8.4, 3.0, 1H, C(12)**H**), 5.90 (dd, *J* = 2.1, 0.9, 1H, C(5)**H**), 5.48 (d, *J* = 2.2, 1H, C(3)**H**), 4.96 (s, 2H, C(8)**H**$_2$), 2.24 (s, 3H, C(7)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6 (q**C**-4), 164.6 (q**C**-2), 163.2 (d, *J* = 249, q**C**-13), 162.7 (q**C**-6), 140.7 (d, *J* = 8, **C**(11)H), 139.0 (d, *J* = 7, q**C**-9), 117.5 (d, *J* = 22, **C**(12)H), 115.9 (d, *J* = 24, **C**(14)H), 100.2 (**C**(5)H), 89.4 (d, *J* = 3, q**C**-10), 88.9 (**C**(3)H), 73.7 (d, *J* = 1, **C**(8)H_2), 19.9 (**C**(7)H_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -113 (s, C(13)**F**); *m/z* (ES+) 361 ($(M+H)^+$ 6%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{11}IFO_3$ 360.9737; Found 360.9741.

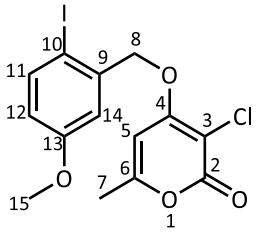
3-Chloro-4-((2-iodo-5-methylbenzyl)oxy)-6-methyl-2*H*-pyran-2-one (51)



Compound **51** was prepared *via* the procedure described for compound **47** using 4-((2-iodo-5-methylbenzyl)oxy)-6-methyl-2*H*-pyran-2-one **48** (200.0 mg, 0.562 mmol, 1.0 equiv.). The residue was purified by column chromatography (MeOH:DCM 0.5:99.5) to yield **51** as a white solid (0.164 g, 75%); m.p. 204–206 °C; IR ν_{max} (film) 1722 (ester C=O stretch), 1638 (alkene C=C stretch), 1544 (aromatic C-C stretch), 1319 (ester C-O stretch), 1239 (ester C-O stretch), 1075 (ether C-O stretch), 743 (C-Cl stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0, 1H, C(11)**H**), 7.28 (d, *J* = 1.3, 1H, C(14)**H**), 6.91 (dd, *J* = 8.0, 1.7, 1H, C(12)**H**), 6.06 (s, 1H,

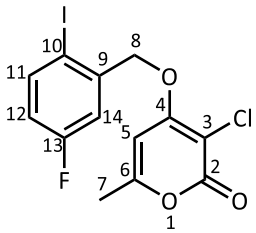
C(5)**H**), 5.17 (s, 2H, C(8)**H**$_2$), 2.34 (s, 3H, C(15)**H**$_3$), 2.29 (s, 3H, C(7)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0 (q**C**-4), 161.8 (q**C**-2), 160.8 (q**C**-6), 139.2 (**C**(11)H), 139.1 (q**C**-9), 136.4 (q**C**-13), 131.3 (**C**(14)H), 129.3 (**C**(12)H), 100.5 (q**C**-3), 96.2 (**C**(5)H), 92.4 (q**C**-10) 75.3 (**C**(8)H_2), 21.1 (**C**(15)H_3), 20.3 (**C**(7)H_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{13}IClO_3$ 390.9598; Found 390.9601.

3-Chloro-4-((2-iodo-5-methoxybenzyl)oxy)-6-methyl-2*H*-pyran-2-one (52)



Compound **52** was prepared *via* the procedure described for compound **47** using an impure sample of 4-((2-iodo-5-methoxybenzyl)oxy)-6-methyl-2*H*-pyran-2-one **49** (0.2 g, 0.537 mmol, 1.0 equiv.), except that the mixture was stirred at 55 °C for 24 h. The residue was purified by column chromatography (MeOH:DCM 0.5:99.5) to yield **52** as a white solid (0.052 g, ~24% based on impure starting material); m.p. 180–184 °C; IR ν_{max} (film) 1719 (ester C=O stretch), 1637 (alkene C=C stretch), 1545 (aromatic C-C stretch), 1318 (ester C-O stretch), 1232 (ester C-O stretch), 1053 (ether C-O stretch), 874 (C-Cl stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.7, 1H, C(11)**H**), 7.08 (d, *J* = 3.0, 1H, C(14)**H**), 6.67 (dd, *J* = 8.7, 3.0, 1H, C(12)**H**), 6.07 (d, *J* = 0.6, 1H, C(5)**H**), 5.16 (s, 2H, C(8)**H**$_2$), 3.80 (s, 3H, C(15)**H**$_3$), 2.29 (d, *J* = 0.6, 3H, C(7)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9 (q**C**-4), 161.9 (q**C**-2), 160.8 (q**C**-6), 160.4 (q**C**-13), 139.9 (**C**(11)H), 137.7 (q**C**-9), 116.4 (**C**(14)H), 114.2 (**C**(12)H), 100.6 (q**C**-3), 96.1 (**C**(5)H), 84.1 (q**C**-10), 75.1 (**C**(8)H_2), 55.5 (**C**(15)H_3), 20.3 (**C**(7)H_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{13}IClO_4$ 406.9547; Found 406.9550.

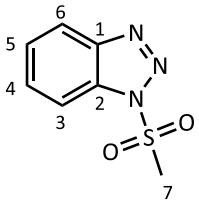
3-Chloro-4-((5-fluoro-2-iodobenzyl)oxy)-6-methyl-2*H*-pyran-2-one (53)



Compound **53** was prepared *via* the procedure described for compound **47** using 4-((5-fluoro-2-iodobenzyl)oxy)-6-methyl-2*H*-pyran-2-one **50** (115 mg, 0.319 mmol, 1.0 equiv.), except that the mixture was stirred at 55 °C for 60 h. The residue was purified by column chromatography (MeOH:DCM 0.5:99.5) to yield **53** as a white solid (0.036 g, 29%); m.p. 221–223 °C; IR ν_{max} (film) 1719 (ester C=O stretch), 1639 (alkene C=C stretch), 1544 (aromatic C-C stretch), 1321 (ester C-

O stretch), 1235 (ester C-O stretch), 1074 (ether C-O stretch), 868 (C-Cl stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.7, 5.4, 1H, C(11)**H**), 7.37 – 7.15 (m, 1H, C(14)**H**), 6.86 (td, *J* = 8.4, 3.0, 1H, C(12)**H**), 6.05 (d, *J* = 0.6, 1H, C(5)**H**), 5.14 (s, 2H, C(8)$\mathbf{H}_2$), 2.31 (d, *J* = 0.7, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5 (q**C**-4), 163.4 (d, *J* = 249, q**C**-13), 161.7 (q**C**-2), 160.6 (q**C**-6), 140.6 (d, *J* = 8, **C**(11)H), 139.0 (d, *J* = 8, q**C**-9), 117.6 (d, *J* = 22, **C**(14)H), 115.8 (d, *J* = 24, **C**(12)H), 100.8 (q**C**-3), 95.9 (**C**(5)H), 88.3 (d, *J* = 3, q**C**-10), 74.6 (d, *J* = 1, **C**(8)H_2), 20.3 (**C**(7)H_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -112 (s, C(13)**F**); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{10}ClFIO_3$ 394.9347; Found 394.9360.

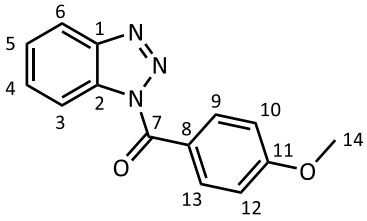
1-(Methylsulfonyl)-1*H*-benzo[*d*][1,2,3]triazole (54)[17]



A 500 mL 3-neck round-bottomed flask was evacuated and refilled with N_2 three times. Benzotriazole (5 g, 42 mmol, 1 equiv.), toluene (100 mL) and anhydrous pyridine (5.4 mL, 67 mmol, 1.6 equiv.) were added to the flask. The stirring, clear solution was cooled to 0 °C. A solution of mesyl chloride (3.9 mL, 50 mmol, 1.2 equiv.) in toluene (50 mL) was prepared and slowly added to the benzotriazole solution. The mixture was stirred at 0 °C for 5 min, then the ice bath was removed and the mixture was left stirring at ambient temperature overnight. The mixture was diluted with H_2O (100 mL) and the layers were separated. The organic components were extracted from the aqueous layer with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (1 × 50 mL) and brine (1 × 50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was recrystallised from toluene to yield **54** as pale yellow crystals (3.9251 g, 47%); m.p. 103–106 °C (lit.[17] 110–111.5 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.4, 1H, C(6)**H**), 8.01 (d, *J* = 8.4, 1H, C(3)**H**), 7.68 (t, *J* = 7.7, 1H, C(4)**H**), 7.54 (t, *J* = 7.7, 1H, C(5)**H**), 3.52 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2 (q**C**-1), 131.7 (q**C**-2), 130.5 (**C**(4)H), 126.1 (**C**(5)H), 120.7 (**C**(6)H), 112.0 (**C**(3)H), 42.9 (**C**(7)H_3); *m/z* (ES+): 198 ($(M+H)^+$ 14%).

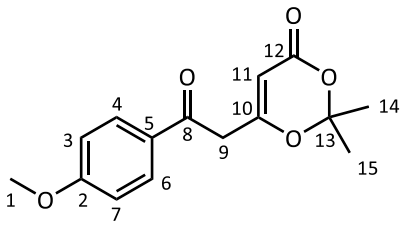
Spectral characteristics were consistent with previously reported data.[18]

(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)(4-methoxyphenyl)methanone (55)



A 50 mL round-bottomed flask was charged with 1-(methylsulfonyl)-1*H*-benzo[*d*][1,2,3]triazole **54** (1.9 g, 9.63 mmol, 1.0 equiv.), 4-methoxybenzoic acid (1.5 g, 9.63 mmol, 1.0 equiv.), Et_3N (1.9 mL, 13.49 mmol, 1.4 equiv.) and THF (25 mL). The flask was placed in an oil bath which was heated to 72 °C. The mixture was stirred at this temperature overnight. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (40 mL) and washed with H_2O (2 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc:hexanes 10:90) to yield **55** as a white solid (1.8 g, 74%); m.p. 101–104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.3, 1H, C(3)**H**), 8.34 – 8.25 (m, 2H, C(9)**H** & C(13)**H**), 8.17 (d, *J* = 8.3, 1H, C(6)**H**), 7.70 (ddd, *J* = 8.2, 7.2, 1.0, 1H, C(4)**H**), 7.55 (ddd, *J* = 8.2, 7.2, 1.0, 1H, C(5)**H**), 7.16 – 6.90 (m, 2H, C(10)**H** & C(12)**H**), 3.94 (s, 3H, C(14)**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7 (q**C**-11), 162.2 (q**C**-7), 145.7 (q**C**-1), 134.4 (**C**(9)H & **C**(13)H), 132.6 (q**C**-2), 130.2 (**C**(4)H), 126.1 (**C**(5)H), 123.5 (q**C**-8), 120.1 (**C**(6)H), 114.9 (**C**(3)H), 113.9 (**C**(10)H & **C**(12)H), 55.6 (**C**(14)H$_3$); *m/z* (ES+): 254 ((M+H)$^+$ 14%).

6-(2-(4-Methoxy)phenyl)-2-oxoethyl)-2,2-dimethyl-4*H*-1,3,-dioxin-4-one (56)[19]

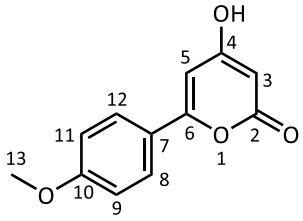


A 50 mL, 2-neck round-bottomed flask fitted with stir bar was heated under vacuum and refilled with N_2 three times. The flask was allowed cool, then freshly distilled THF (5 mL) was added. The THF was cooled to -78 °C. LDA (8.0 mL, 1.0 M in THF/hexanes, 1.15 equiv.) was added. The solution was stirred at -78 °C for 15 min. A solution of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (1.0 mL, 7.90 mmol, 1.13 equiv.) in freshly distilled THF (5 mL) was added dropwise to the LDA solution over 30 min. The mixture was then stirred at -78 °C for 4 h. A suspension of (1*H*-benzo[d][1,2,3]triazol-1-yl)(4-methoxyphenyl)methanone **55** (1.8 g, 6.96 mmol, 1 equiv.) in freshly distilled THF (10 mL) was added to the reaction and the mixture was stirred for 30 min at -78 °C, then left to warm to

ambient temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl (2 mL) and concentrated under reduced pressure. The residue was diluted with H_2O (50 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with saturated aqueous Na_2CO_3 (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc:hexanes 0:100 → 70:30) to give **56** as an oily yellow solid (0.169, 6%); m.p. 57–59 °C (lit.[19] 82 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 9.0, 2H, C(3)**H** & C(7)**H**), 6.96 (d, *J* = 9.0, 2H, C(4)**H** & C(6)**H**), 5.42 (s, 1H, C(11)**H**), 3.88 (s, 3H, C(1)**H**$_3$), 3.86 (s, 2H, C(9)**H**), 1.70 (s, 6H, C(14)**H**$_3$ & C(15)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5 (q**C**-8), 165.7 (q**C**-12), 164.2 (q**C**-2), 161.0 (q**C**-10), 130.7 (**C**(4)H & **C**(6)H), 128.9 (q**C**-5), 114.1 (**C**(3)H & **C**(7)H), 107.3 (q**C**-13), 96.8 (**C**(11)H), 55.6 (**C**(1)H$_3$), 43.0 (**C**(9)H$_2$), 25.0 (**C**(14)H$_3$ & **C**(15)H$_3$); *m/z* (ES-): 275 ($(M-H)^-$ 70%).

Spectral characteristics were consistent with previously reported data.[19]

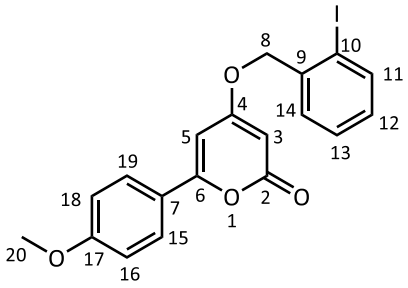
4-Hydroxy-6-(4-methoxyphenyl)-2*H*-pyran-2-one (57)[7]



Compound **57** was prepared *via* the procedure described for compound **8** using 6-(2-(4-methoxy)phenyl)-2-oxoethyl)-2,2-dimethyl-4*H*-1,3,-dioxin-4-one **56** (146 mg, 0.532 mmol, 1.0 equiv.) as the starting material. The resulting crude product was purified by column chromatography (acetone:DCM 30:70) to yield the pure product **57** as an off-white solid (0.068 g, 59%); m.p. 196–199 °C (lit.[7] 193–195 °C); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.89 – 7.81 (m, 2H, C(8)**H** & C(12)**H**), 7.12 – 7.03 (m, 2H, C(9)**H** & C(11)**H**), 6.58 (d, *J* = 2.1, 1H, C(5)**H**), 5.41 (d, *J* = 2.0, 1H, C(3)**H**), 3.90 (s, 3H, C(13)**H**$_3$); ^{13}C NMR (75 MHz, acetone-d_6) δ 170.3 (q**C**-2), 163.0 (q**C**-4), 162.0 (q**C**-7), 161.1 (q**C**-6), 127.3 (**C**(8)H & **C**(12)H), 124.0 (q**C**-10), 114.3 (**C**(9)H & **C**(11)H), 96.0 (**C**(5)H), 89.1 (**C**(3)H), 55.0 (**C**(13)H$_3$); *m/z* (ES+): 219 ($(M+H)^+$ 32%).

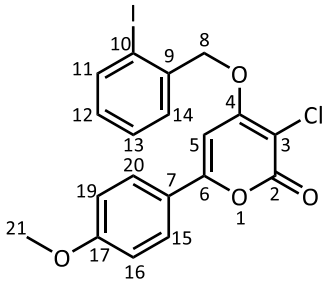
Spectral characteristics were consistent with the previously reported data.[7]

4-((2-Iodobenzyl)oxy)-6-(4-methoxyphenyl)-2*H*-pyran-2-one (58)



Compound **50** was prepared *via* the procedure described for compound **4** using 4-hydroxy-6-(4-methoxyphenyl)-*2H*-pyran-2-one **57** (65 mg, 0.298 mmol, 1.0 equiv.) and 2-iodobenzyl bromide **2** (106 mg, 0.357 mmol, 1.2 equiv.). The residue was purified by column chromatography (MeOH:DCM 0.5:99.5) to yield **58** as an orange solid (0.054 g, 42%); m.p. 107–109 °C; IR ν_{max} (film) 1720 (C=O stretch), 1634 (alkene C=C stretch), 1510 (aromatic C–C stretch), 1178 (C–O stretch), 752 (C–I stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 7.9, 1.0, 1H, ArC**H**), 7.84 – 7.72 (m, 2H, 2 × ArC**H**), 7.50 – 7.35 (m, 2H, 2 × ArC**H**), 7.14 – 7.03 (m, 1H, ArC**H**), 7.01 – 6.90 (m, 2H, 2 × ArC**H**), 6.41 (d, *J* = 2.1, 1H, C(5)**H**), 5.58 (d, *J* = 2.1, 1H, C(3)**H**), 5.06 (s, 2H, C(8)$\mathbf{H}_2$), 3.85 (s, 3H, C(20)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3 (q**C**-4), 164.2 (q**C**-2), 162.0 (q**C**-17), 160.6 (q**C**-6), 139.7 (Ar**C**H), 136.9 (q**C**-9), 130.4 (Ar**C**H), 129.1 (Ar**C**H), 128.6 (Ar**C**H), 127.4 (**C**(15)H & **C**(19)H), 123.6 (q**C**-7), 114.3 (**C**(16)H & **C**(18)H), 97.8 (q**C**-10), 96.3 (**C**(5)H), 89.0 (**C**(3)H), 74.5 (**C**(8)H_2), 55.5 (**C**(20)H_3); *m/z* (ES-): 433 ($(M-H)^-$ 14%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{16}O_4I$ 435.0093; Found 435.0095.

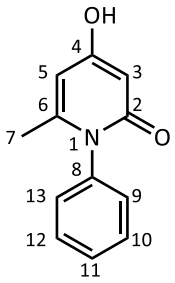
3-Chloro-4-((2-iodobenzyl)oxy)-6-(4-methoxyphenyl)-2*H*-pyran-2-one (59)



Compound **59** was prepared *via* the procedure described for compound **47** using 4-((2-iodobenzyl)oxy)-6-(4-methoxyphenyl)-2*H*-pyran-2-one **58** (150.0 mg, 0.345 mmol, 1.0 equiv.), except that the mixture was stirred at 55 °C for 60 h. The residue was purified by column chromatography (MeOH:DCM 0.5:99.5) to yield **59** as a yellow solid (0.080 g, 49%); m.p. 183–185 °C; IR ν_{max} (film) 1713 (ester C=O stretch), 1625 (alkene C=C stretch), 1507 (aromatic C-C stretch), 1265 (ester C-O stretch), 1180 (ether C-O stretch), 1107 (alkene C-H bend), 738 (C-Cl stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.9, 1H, C(11)**H**), 7.81 – 7.71 (m, 2H, C(15)**H** & C(20)**H**), 7.54 (d, *J* = 7.7, 1H, C(14)**H**), 7.44 (t, *J* = 7.5, 1H, C(13)**H**), 7.09 (t, *J* = 7.6, 1H, C(12)**H**), 6.96 (d, *J* = 8.9, 2H, C(16)**H** & C(19)**H**), 6.53 (s, 1H, C(5)**H**), 5.33 (s, 2H, C(8)$\mathbf{H}_2$), 3.87 (d, *J* = 1.2, 3H, C(21)$\mathbf{H}_3$); ^{13}C NMR (75

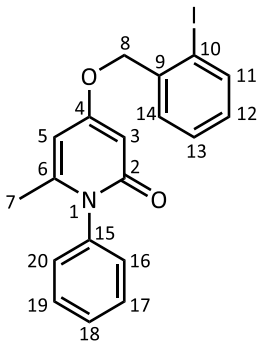
MHz, $CDCl_3$) δ 164.3 (q**C**-4), 162.4 (q**C**-2), 160.3 (q**C**-17), 159.8 (q**C**-6), 139.5 (**C**(11)H), 136.9 (q**C**-9), 130.4 (C(12)H), 129.0 (C(14)H), 128.6 (C(13)H), 127.7 (**C**(15)H & **C**(20)H), 123.0 (q**C**-7), 114.5 (**C**(16)H & **C**(19)H), 100.7 (q**C**-3), 96.6 (q**C**-10), 91.8 (**C**(5)H), 75.3 (**C**(8)H_2), 55.5 (**C**(21)H_3); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{15}IClO_3$ 468.9704; Found 468.9715.

4-Hydroxy-6-methyl-1-phenylpyridin-2(1*H*)-one (60)[20]



Compound **60** was prepared *via* the procedure described for compound **13** using 4-hydroxy-6-methyl-2*H*-pyran-2-one **3** (5.0 g, 39.65 mmol, 1.0 equiv.) and aniline (3.6 mL, 39.65 mmol, 1.0 equiv.) to yield **60** as a pale yellow solid (1.8407 g, 23%) after trituration in EtOH; m.p. >250 °C (lit.[20] 277–278 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.60 (br s, 1H, O–**H**), 7.64 – 7.33 (m, 3H, C(10)**H**, C(11)**H** & C(12)**H**), 7.32 – 7.04 (m, 2H, C(9)**H** & C(13)**H**), 5.89 (d, *J* = 1.7, 1H, C(5)**H**), 5.56 (d, *J* = 2.4, 1H, C(3)**H**), 1.83 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.9 (q**C**-4), 164.6 (q**C**-2), 147.4 (q**C**-6), 139.3 (q**C**-8), 129.7 (**C**(10)H & **C**(12)H), 129.1 (**C**(9)H & **C**(13)H), 128.6 (**C**(11)H), 100.5 (**C**(5)H), 96.6 (**C**(3)H), 21.5 (**C**(7)H_3); *m/z* (ES+): 202 ($(M+H)^+$ 100%).

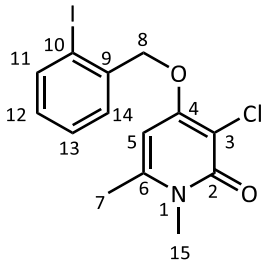
4-((2-Iodobenzyl)oxy)-6-methyl-1-phenylpyridin-2(1*H*)-one (61)



Compound **61** was prepared *via* the procedure described for compound **15** using 4-hydroxy-6-methyl-1-phenylpyridin-2(1*H*)-one **60** (0.50 g, 2.48 mmol, 1.0 equiv.) and 2-iodobenzylbromide **2** (0.83 g, 2.78 mmol, 1.12 equiv.). The residue was purified by column chromatography (EtOAc:hexanes 70:30) to yield **61** as a yellow solid (0.805 g, 78%); m.p. 120–124 °C; IR ν_{max} (film) 1662 (amide C=O stretch), 1590 (alkene C=C stretch), 1558 (aromatic C–C stretch), 1241 (ether C–O stretch), 1118 (C–N stretch), 1044 (alkene C–H bend); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.9, 0.8, 1H, ArC**H**), 7.59 – 7.32 (m, 5H, 5 × ArC**H**), 7.24 – 7.15 (m, 2H, 2 × ArC**H**), 7.05 (td, *J* = 7.7, 1.7, 1H, ArC**H**), 6.00 (d, *J* = 2.6, C(5)**H**), 5.96 (d, *J* = 1.9, C(3)**H**), 5.01 (s, 2H, C(8)$\mathbf{H}_2$), 1.92 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (q**C**-4), 165.4 (q**C**-2), 146.4 (q**C**-6), 139.5 (Ar**C**H), 138.6 (q**C**-15), 137.8 (q**C**-9), 129.9 (Ar**C**H), 129.7 (2 × Ar**C**H), 128.8 (Ar**C**H),

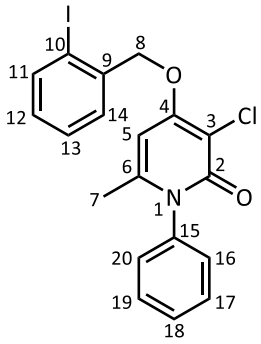
128.7 (Ar**C**H), 128.5 (Ar**C**H), 128.3 (2 × Ar**C**H), 100.8 (**C**(5)H), 97.6 (q**C**-10), 96.4 (**C**(3)H), 73.9 (**C**(8)H_2), 21.5 (**C**(7)H_3); *m/z* (ES+): 418 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{17}INO_2$ 418.0304; Found 418.0307.

3-Chloro-4-((2-iodobenzyl)oxy)-1,6-dimethylpyridin-2(1*H*)-one (62)



Compound **62** was prepared *via* the procedure described for compound **47** using 4-((2-iodobenzyl)oxy)-1,6-dimethylpyridin-2(1*H*)-one **16** (200 mg, 0.563 mmol, 1.0 equiv.), except that the mixture was stirred at 55 °C for 24 h. The residue was purified by recrystallisation from EtOH to yield **62** as a white solid (0.1092 g, 50 %); m.p. 170–171 °C; IR ν_{max} (film) 1569 (C=O stretch), 1635 (alkene C=C stretch), 1600 (aromatic C–C stretch), 1019 (C–N stretch), 735 (C–X stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.9, 1.1, 1H, C(11)**H**), 7.55 (dt, *J* = 7.7, 0.7, 1H, C(14)**H**), 7.40 (td, *J* = 7.6, 1.2, 1H, C(13)**H**), 7.05 (td, *J* = 7.6, 1.8, 1H, C(12)**H**), 5.95 (d, *J* = 0.6, 1H, C(5)**H**), 5.14 (s, 2H, C(8)$\mathbf{H}_2$), 3.56 (s, 3H, C(15)$\mathbf{H}_3$), 2.36 (d, *J* = 0.6, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9 (q**C**-4), 160.6 (q**C**-2), 145.2 (q**C**-6), 139.2 (Ar**C**H), 137.7 (q**C**-9), 129.9 (Ar**C**H), 128.7 (Ar**C**H), 128.3 (Ar**C**H), 106.4 (q**C**-3), 96.2 (q**C**-10), 95.9 (**C**(5)H), 74.4 (**C**(8)H_2), 32.0 (**C**(15)H_3), 21.4 (**C**(7)H_3); *m/z* (ES−): 388 ($(M-H)^-$ 10%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{14}NO_2ICl$ 389.9758; Found 389.9761.

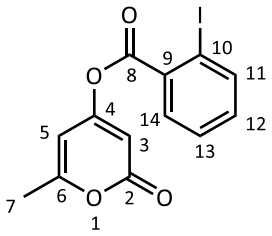
3-Chloro-4-((2-iodobenzyl)oxy)-6-methyl-1-phenylpyridin-2(1*H*)-one (63)



Compound **63** was prepared *via* the procedure described for compound **47** using 4-((2-iodobenzyl)oxy)-6-methyl-1-phenylpyridin-2(1*H*)-one **61** (0.69 g, 1.654 mmol, 1.0 equiv.), except that the mixture was stirred at 55 °C for 42 h. The residue was purified by column chromatography (EtOAc:hexanes 90:10) to give a yellow solid which was triturated in EtOH to yield **63** as a yellow solid (0.1152 g, 15%); m.p. 239–243 °C; IR ν_{max} 1654 (amide C=O stretch), 1531 (aromatic C–C stretch), 1350 (ether C–O stretch, 1222 (C–N stretch), 1052 (alkene C–H bend), 751 (C–Cl stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.9, 0.9, 1H, ArC**H**), 7.60 (d, *J* = 7.7, 1H, ArC**H**), 7.55 – 7.37 (m,

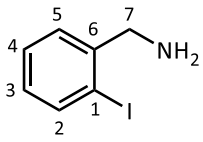
4H, 4 × ArC**H**), 7.22 – 7.13 (m, 2H, 2 × ArC**H**), 7.07 (td, *J* = 7.8, 1.6, 1H, ArC**H**), 6.05 (s, 1H, C(5)**H**), 5.20 (s, 2H, C(8)$\mathbf{H}_2$), 1.98 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2 (q**C**-4), 161.0 (q**C**-2), 145.3 (q**C**-6), 139.3 (Ar**C**H), 138.5 (q**C**-15), 137.7 (q**C**-9), 129.9 (Ar**C**H), 129.8 (2 × Ar**C**H), 129.0 (Ar**C**H), 128.8 (Ar**C**H), 128.4 (Ar**C**H), 127.9 (2 × Ar**C**H), 106.8 (q**C**-3), 96.2 (q**C**-10), 95.9 (**C**(5)H), 74.6 (**C**(8)H_2), 22.0 (**C**(7)H_3); *m/z* (ES+): 452 (^{35}Cl (M+H)$^+$ 100%), 454 (^{37}Cl (M+H)$^+$ 38%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{19}H_{16}IClNO_2$ 451.9914; Found 451.9918.

6-Methyl-2-oxo-2*H*-pyran-4-yl 2-iodobenzoate (74)



Using a procedure based on the Steglich esterification,[21] a solution of 4-hydroxy-6-methyl-2*H*-pyran-2-one **3** (0.40 g, 3.17 mmol, 2.0 equiv.), 2-iodobenzoic acid (0.49 g, 1.586 mmol, 1.0 equiv.), *N,N'*-dicyclohexylcarbodiimide (DCC) (0.36 g, 1.744 mmol, 1.1 equiv.) and 4-dimethylaminopyridine (DMAP) (9.7 mg, 0.079 mmol, 5 mol%) in DCM (10 mL) was stirred at ambient temperature for 24 h. The solids were then removed by gravity filtration through fluted filter paper. The solids were washed with DCM. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc:hexanes 30:70) to give **74** as a cream solid (0.457 g, 81%); m.p. 112–113 °C; IR ν_{max} (film) 1736 (ester C=O stretch), 1638 (alkene C=C stretch), 1561 (aromatic C–C stretch), 1238 (ester C–O stretch), 1213 (ester C–O stretch), 1010 (ester C–O stretch), 729 (C–I stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.0, 1H, C(11)**H**), 7.97 (dd, *J* = 8.0, 1.5, 1H, C(14)**H**), 7.50 (t, *J* = 7.6, 1H, C(13)**H**), 7.27 (td, *J* = 7.4, 1.4, 1H, C(12)**H**), 6.23 – 6.17 (m, 1H, C(5)**H**), 6.16 – 6.08 (m, 1H, C(3)**H**), 2.31 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6 (q**C**-4 & q**C**-8), 163.1 (q**C**-2), 162.3 (q**C**-6), 142.1 (**C**(11)H), 134.2 (**C**(12)H), 132.3 (q**C**-9), 132.0 (**C**(14)H), 128.3 (**C**(13)H), 101.5 (**C**(5)H), 101.3 (**C**(3)H), 95.0 (q**C**-10), 20.2 (**C**(7)H_3); *m/z* (ES+): 357 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{13}H_{10}O_4I$ 356.9624; Found 356.9620.

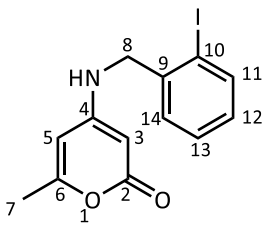
(2-Iodophenyl)methanamine (77)[22]



This compound was prepared according to the literature procedure.[22] A 2-neck round-bottomed flask was heated under vacuum and refilled with N_2 three times. 2-Iodobenzonitrile **76** (1.15 g, 5.00 mmol, 1.0 equiv.) was added and the flask was evacuated and refilled with N_2 three times. Freshly distilled THF (10 mL) was added *via* syringe. The stirring solution was cooled to 0 °C. A solution of BH_3.THF (10 mL, 1.0 M, 2.0 equiv.) was added slowly over 10 min to the stirring solution. The reaction mixture was maintained at 0 °C for 5 min once the addition was complete. The ice bath was removed and the mixture was stirred at ambient temperature for 24 h under nitrogen. The reaction was again cooled to 0 °C and H_2O (20 mL) was slowly added dropwise to quench the reaction. The mixture was transferred to a round-bottomed flask and the THF was removed under reduced pressure. 10% (w/v) aqueous NaOH (2 mL) was added to make the aqueous solution alkaline (~pH 10). The organic component was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (MeOH:DCM 5:95) to yield **77** as a clear oil (0.3413 g, 29%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.8, 1.0, 1H, C(2)**H**), 7.40 – 7.28 (m, 2H, C(4)**H** & C(5)**H**), 6.99 – 6.88 (m, 1H, C(3)**H**), 3.85 (s, 2H, C(7)$\mathbf{H}_2$), 1.53 (br s, 2H, N$\mathbf{H}_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2 (q**C**-6), 139.5 (**C**(2)H), 128.6 (**C**(5)H), 128.6 (**C**(3)H), 128.5 (**C**(4)H), 99.0 (q**C**-1), 51.4 (**C**(7)H_2); *m/z* (ES+): 234 ($(M+H)^+$ 100%).

Spectral characteristics were consistent with previously reported data.[22]

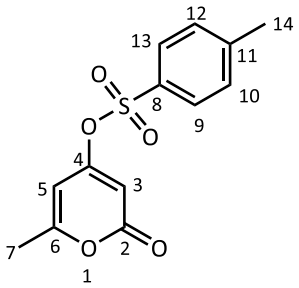
4-*N*-((2-Iodobenzyl)amino)-6-methyl-*2H*-pyran-2-one (78)



Based on a literature procedure,[23] a solution of 2-iodobenzylamine **77** (260 mg, 1.12 mmol, 2.5 equiv.) in dried EtOH (2 mL) was added to a Schlenk tube containing 4-bromo-6-methyl-2*H*-pyran-2-one **6** (84 mg, 0.45 mmol, 1.0 equiv.) and set stirring. The Schlenk tube was placed in an oil bath which was heated to 85 °C. The reaction was stirred at this temperature for 20 h, then cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by

column chromatography (acetone:hexanes 40:60 → 50:50) to give **78** as a yellow solid (0.15 g, 85%); m.p. 186–189 °C; IR ν_{max} (film) 3248 (N–H stretch), 1678 (C=O stretch), 1551 (N–H bend); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.90 (dd, *J* = 7.8, 1.1, 1H, C(11)**H**), 7.72 (t, *J* = 5.3, 1H, N–**H**), 7.42 (td, *J* = 7.4, 1.1, 1H, C(13)**H**), 7.30 (dd, *J* = 7.8, 1.4, 1H, C(14)**H**), 7.08 (td, *J* = 7.6, 1.8, 1H, C(12)**H**), 5.88 (s, 1H, C(5)**H**), 4.63 (s, 1H, C(3)**H**), 4.24 (d, *J* = 5.3, 2H, C(8)**H**$_2$), 2.09 (s, 3H, C(7)**H**$_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.8 (q**C**-4), 160.7 (q**C**-2), 158.2 (q**C**-6), 139.8 (**C**(11)H), 139.5 (q**C**-9), 130.0 (**C**(13)H), 129.3 (**C**(12)H), 129.0 (**C**(14)H), 99.8 (q**C**-10), 99.1 (**C**(5)H), 79.5 (**C**(3)H), 51.1 (**C**(8)H$_2$), 19.9 (**C**(7)H$_3$); *m/z* (ES+): 342 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{13}H_{13}NO_2I$ 341.9991; Found 341.9993.

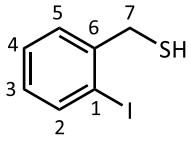
6-Methyl-4-(*p*-toluenesulfonyloxy)-2*H*-pyran-2-one (80)[24]



A solution of 4-hydroxy-6-methyl-2*H*-pyran-2-one **3** (2.0 g, 15.86 mmol, 1.0 equiv.), *p*-tosyl chloride (3.6 g, 19.03 mmol, 1.2 equiv.) and Et_3N (2.7 mL, 19.03 mmol, 1.2 equiv.) in DCM (60 mL) was stirred at ambient temperature for 30 min. The reaction mixture was concentrated under reduced pressure to give a cream solid, which was recrystallised from DCM/hexanes to give **80** as a cream solid (3.726 g, 84%); m.p. 103–104 °C (lit.[24] 100–102 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 – 7.66 (m, 2H, C(10)**H** & C(12)**H**), 7.44 – 7.35 (m, 2H, C(9)**H** & C(13)**H**), 6.03 – 5.97 (m, 1H, C(5)**H**), 5.83 – 5.78 (m, 1H, C(3)**H**), 2.48 (s, 3H, C(14)**H**$_3$), 2.24 (s, 3H, C(7)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3 (q**C**-4), 162.8 (q**C**-2), 162.0 (q**C**-6), 146.7 (q**C**-8), 131.7 (q**C**-11), 130.3 (**C**(10)H & **C**(12)H), 128.4 (**C**(9)H & **C**(13)H), 100.7 (**C**(5)H), 100.7 (**C**(3)H), 21.8 (**C**(14)H$_3$), 20.2 (**C**(7)H$_3$); *m/z* (ES+): 281 ((M+H)$^+$ 80%).

Spectral characteristics were consistent with previously reported data.[24]

(2-Iodophenyl)methanethiol (81)[25]

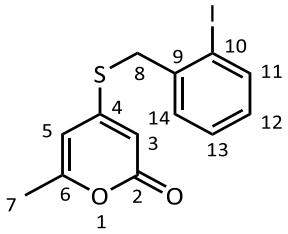


Modifying a procedure described for benzenethiol,[26] a mixture of 2-iodobenzyl bromide **2** (0.54 g, 1.82 mmol, 1.0 equiv.), thiourea (0.18 g, 2.36 mmol, 1.3 equiv.) and H_2O (5 mL) were placed in a

Schlenk tube and heated to 100 °C with vigorous stirring until the thiourea dissolved. The resulting clear solution was refluxed for 2 h. A solution of NaOH (0.23 g, 5.75 mmol, 3.0 equiv.) in H_2O (2 mL) was then added to the mixture, turning it cloudy. This mixture was refluxed for a further 2 h, then cooled to ambient temperature. The reaction mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with 1 M aqueous HCl (1 × 20 mL) and H_2O (1 × 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give **81** as a clear yellow oil (0.292 g, 64%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.8, 1H, C(2)**H**), 7.41 – 7.27 (m, 2H, C(3)**H** & C(5)**H**), 6.92 (td, *J* = 7.6, 1.8, 1H, C(4)**H**), 3.81 (d, *J* = 8.1, 2H, C(7)**H**$_2$), 2.00 (t, *J* = 8.1, 1H, S–**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7 (q**C**-6), 139.8 (**C**(2)H), 129.2 (**C**(5)H), 128.9 (**C**(3)H), 128.8 (**C**(4)H), 99.3 (q**C**-1), 34.6 (**C**(7)H_2); *m/z* (ES+): 217 ((M-SH)$^+$ 4%).

Spectral characteristics were consistent with previously reported data.[25]

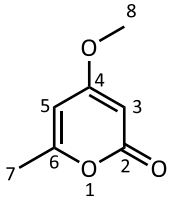
4-((2-Iodobenzyl)thio)-6-methyl-2*H*-pyran-2-one (82)



Based on a literature procedure,[27] a Schlenk tube was heated under vacuum and refilled with N_2 three times. 2-Iodobenzylthiol **81** (257 mg, 1.03 mmol, 1.10 equiv.) and methanol (5 mL) were added through a syringe and the solution was stirred. Small pieces of sodium metal (without oil washed off) (22 mg, 0.953 mmol, 1.02 equiv.) were added to the stirring solution. Once the sodium had dissolved to give a clear yellow solution, 4-tosyloxy-6-methyl-2*H*-pyran-2-one **80** (262 mg, 0.935 mmol, 1.00 equiv.) was added under a positive pressure of N_2 to give a cloudy suspension. The flask was lowered into an oil bath and heated to 70 °C with stirring. The pyrone dissolved giving a clear yellow solution. The reaction mixture was stirred at 70 °C for 4 h. The mixture was cooled to ambient temperature and H_2O (10 mL) was added. The mixture was extracted with DCM (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc:hexanes 30:70) to give **82** as a yellow solid (0.166 g, 50%); m.p. 111–115 °C; IR ν_{max} (film) 1712 (ester C=O stretch), 1634 (alkene C=C stretch), 1528 (aromatic C–

C stretch), 1309 (ester C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.0, 0.9, 1H, C(11)**H**), 7.44 (dd, *J* = 7.7, 1.5, 1H, C(14)**H**), 7.34 (td, *J* = 7.5, 0.9, 1H, C(12)**H**), 7.01 (td, *J* = 7.7, 1.6, 1H, C(13)**H**), 5.88 (s, 1H, C(5)**H**), 5.86 (s, 1H, C(3)**H**), 4.22 (s, 2H, C(8)$\mathbf{H}_2$), 2.20 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3 (q**C**-2), 160.2 (q**C**-6), 158.6 (q**C**-4), 140.1 (**C**(11)H), 136.6 (q**C**-9), 130.0 (**C**(14)H), 129.8 (**C**(12)H), 128.9 (**C**(13)H), 103.2 (**C**(5)H), 103.1 (**C**(3)H), 100.5 (q**C**-10), 40.9 (**C**(8)H_2), 19.8 (**C**(7)H_3); *m/z* (ES+): 359 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{12}O_2IS$ 358.9603; Found 358.9601.

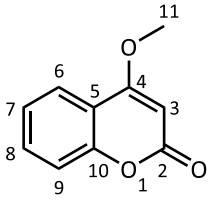
4-Methoxy-6-methyl-2*H*-pyran-2-one (90)[28]



Following the literature procedure,[28] trimethylphosphate (9.8 mL, 83.2 mmol, 2.1 equiv.) was added to a 100 mL round-bottomed flask containing 4-hydroxy-6-methyl-2*H*-pyran-2-one **3** (5.0 g, 39.6 mmol, 1.0 equiv.) and K_2CO_3 (6.6 g, 47.5 mmol, 1.2 equiv.). The flask was placed in an oil bath preheated to 140 °C and stirred at this temperature for 3 h. While the mixture was warm, it was transferred to a separating funnel with H_2O (50 mL). Extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was recrystallised from EtOH to give **90** as a yellow solid (2.5263 g, 46%); m.p. 85–87 °C (lit.[28] 85–87 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (dd, *J* = 2.1, 0.9, 1H, C(5)**H**), 5.41 (d, *J* = 2.2, 1H, C(3)**H**), 3.80 (s, 3H, C(8)$\mathbf{H}_3$), 2.21 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3 (q**C**-4), 165.0 (q**C**-2), 162.1 (q**C**-6), 100.4 (**C**(5)H), 87.3 (**C**(3)H), 55.8 (**C**(8)H_3), 19.8 (**C**(7)H_3); *m/z* (ES+): 141 ($(M+H)^+$ 98%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_7H_9O_3$ 141.0552; Found 141.0553.

Spectral characteristics were consistent with previously reported data.[28]

4-Methoxy-2*H*-chromen-2-one (91)[29]

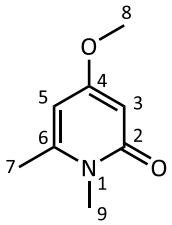


Compound **91** was prepared *via* the procedure described for compound **90** using 4-hydroxy-2*H*-chromen-2-one **19** (5.0 g, 30.837 mmol, 1.0 equiv.), except that the mixture was stirred at 140 °C for 1 h. The residue was recrystallised from EtOH to yield **91** as an off-white solid (4.6932 g, 86%); m.p. 116–118 °C (lit.[29] 122–124 °C); ^{1}H NMR

(300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.9, 1.5, 1H, ArC**H**), 7.55 (ddd, *J* = 8.6, 7.4, 1.6, 1H, ArC**H**), 7.36 – 7.22 (m, 2H, 2 × ArC**H**), 5.70 (s, 1H, C(3)**H**), 4.00 (s, 3H, C(11)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5 (q**C**-4), 162.9 (q**C**-2), 153.3 (q**C**-10), 132.4 (Ar**C**H), 123.9 (Ar**C**H), 123.0 (Ar**C**H), 116.8 (Ar**C**H), 115.6 (q**C**-5), 90.1 (**C**(3)H), 56.4 (**C**(11)H_3); *m/z* (ES+): 177 ($[M+H]^+$ 100%).

Spectral characteristics were consistent with previously reported data.[29]

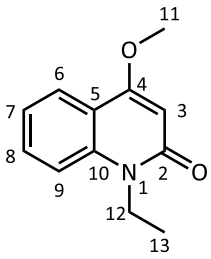
4-Methoxy-1,6-dimethylpyridin-2(1*H*)-one (92)[30]



Compound **92** was prepared *via* the procedure described for compound **90** using 4-hydroxy-1,6-dimethylpyridin-2(1*H*)-one **13** (5.0 g, 35.931 mmol, 1.0 equiv.), except that the mixture was stirred at 140 °C for 18 h. The residue was recrystallised from DCM/hexanes to yield **92** as a yellow solid (3.1936 g, 58%); m.p. (EtOH) 56–58 °C (lit.[30] (C_6H_6) 115–116 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (d, *J* = 2.8, 1H, C(5)**H**), 5.79 – 5.74 (m, 1H, C(3)**H**), 3.74 (s, 3H, (C(8)$\mathbf{H}_3$), 3.46 (s, 3H, C(9)$\mathbf{H}_3$), 2.30 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2 (q**C**-4), 165.4 (q**C**-2), 146.0 (q**C**-6), 100.7 (**C**(5)H), 94.5 (**C**(3)H), 55.2 (**C**(8)H_3), 30.5 (**C**(9)H_3), 20.9 (**C**(7)H_3); *m/z* (ES+): 154 ($[M+H]^+$ 100%).

Spectral characteristics were consistent with previously reported data.[30]

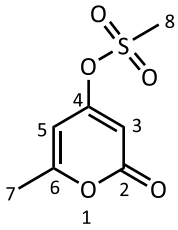
1-Ethyl-4-methoxyquinolin-2(1*H*)-one (94)



Compound **94** was prepared *via* the procedure described for compound **90** using 1-ethyl-4-hydroxyquinolin-2(1*H*)-one **93** (0.5 g, 2.64 mmol, 1.0 equiv.), except that the mixture was stirred at 140 °C for 2 h. The residue was recrystallised from EtOH to yield **94** as an orange solid (0.3534 g, 66%); m.p. 60–63 °C; IR ν_{max} (film) 2981 (aromatic C–H stretch), 1634 (amide C=O stretch), 1575 (aromatic C=C stretch), 1324 (ether C–O stretch), 1122 (amide C–N stretch); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.0, 1.5, 1H, C(6)**H**), 7.58 (ddd, *J* = 9.6, 7.2, 1.6, 1H, C(8)**H**), 7.36 (d, *J* = 8.6, 1H, C(9)**H**), 7.21 (td, *J* = 7.6, 0.7, 1H, C(7)**H**), 6.03 (s, 1H, C(3)**H**), 4.33 (q, *J* = 7.1, 2H, C(12)$\mathbf{H}_2$), 3.94 (s, 3H, C(11)$\mathbf{H}_3$), 1.34 (t, *J* = 7.1, 3H, C(13)$\mathbf{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (q**C**-4), 162.6 (q**C**-2), 138.7 (q**C**-10), 131.2 (Ar**C**H), 123.6 (Ar**C**H), 121.4 (Ar**C**H),

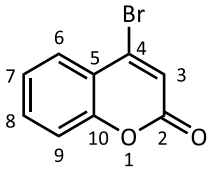
116.7 (q**C**-5), 113.9 (Ar**C**H), 96.5 (**C**(3)H), 55.8 (**C**(11)H_3), 36.8 (**C**(12)H_2), 12.9 (**C**(13)H_3); *m/z* (ES+): 204 ([M+H]$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{12}H_{14}O_2N$ 204.1025; Found 204.1023.

6-Methyl-2-oxo-2*H*-pyran-4-yl methanesulfonate (95)



A stirring suspension of 4-hydroxy-2*H*-pyran-2-one **3** (2.0 g, 15.86 mmol, 1.0 equiv.) and K_2CO_3 (2.6 g, 19.03 mmol, 1.2 equiv.) in acetone (50 mL) was stirred at ambient temperature for 10 min. Mesyl chloride (1.5 mL, 19.03 mmol, 1.2 equiv.) was added, and the mixture was stirred at ambient temperature for 2 h. The reaction mixture was concentrated under reduced pressure to give a yellow solid, which was recrystallised from EtOH to give **95** as an off-white solid (2.6189 g, 81%); m.p. 84–85 °C; IR ν_{max} (film) 1720 (ester C=O stretch)), 1646 (alkene C=C stretch), 1571 (aromatic C–C stretch), 1372 (ester C–O stretch), 1319 (ether C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (s, 2H, C(3)**H** & C(5)**H**), 3.28 (s, 3H, C(8)**H**$_3$), 2.30 (s, 3H, C(7)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7 (q**C**-4), 162.7 (q**C**-2), 161.4 (q**C**-6), 100.2 (**C**(5)H), 100.2 (**C**(3)H), 39.0 (**C**(8)H_3), 20.2 (**C**(7)H_3); *m/z* (ES+): 205 ((M+H)$^+$ 30%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_7H_9O_5S$ 205.0171; Found 205.0168.

4-Bromo-2*H*-chromen-2-one (96)[31]

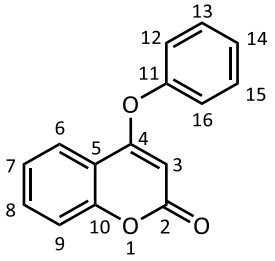


To a 250 mL round-bottomed flask were added 4-hydroxy-2*H*-chromen-2-one **19** (3.0 g, 18.50 mmol, 1.0 equiv.), TBAB (6.9 g, 21.46 mmol, 1.16 equiv.), P_2O_5 (6.3 g, 44.40 mmol, 2.4 equiv.) and toluene (75 mL). The flask was fitted with a condenser and placed in an oil bath preheated to 100 °C. The reaction mixture was stirred at this temperature for 1.5 h, then cooled to ambient temperature. The organic layer was separated from the viscous inorganic layer. The inorganic layer was washed with toluene (2 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (60 mL) and brine (80 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield **96** as a yellow solid (2.946 g, 71%); m.p. 87–90 °C (lit.[31] 88–89 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 7.9, 1.5, 1H, ArC**H**), 7.74 – 7.49 (m, 1H, ArC**H**), 7.44 – 7.29 (m, 2H, 2 × ArC**H**), 6.87 (s, 1H, C(3)**H**); ^{13}C NMR (75

MHz, $CDCl_3$) δ 158.7 (q**C**-2), 152.5 (q**C**-10), 141.4 (q**C**-4), 133.2 (Ar**C**H), 128.0 (Ar**C**H), 124.9 (Ar**C**H), 119.6 (Ar**C**H), 119.0 (q**C**-5), 117.0 (**C**(3)H); *m/z* (ES+): 225 (^{79}Br $(M+H)^+$ 60%), 227 (^{81}Br $(M+H)^+$ 56%).

Spectral characteristics were consistent with previously reported data.[31]

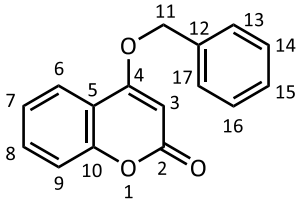
4-Phenoxy-2*H*-chromen-2-one (97)[31]



To a 100 mL round-bottomed flask were added 4-bromo-2*H*-chromen-2-one **96** (1.5 g, 6.67 mmol, 1.0 equiv.), phenol (0.7 g, 7.33 mmol, 1.1 equiv.), K_2CO_3 (1.7 g, 12.00 mmol, 1.8 equiv.) and acetone (35 mL). The flask was fitted with a condenser and placed in an oil bath preheated to 65 °C. The reaction mixture was stirred at this temperature overnight, then cooled to ambient temperature. The mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with 10% (w/v) aqueous NaOH (3 × 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield **97** as a light brown solid (1.3812 g, 87%); m.p. 130–133 °C (lit.[31] 131–132 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 7.9, 1.2, 1H, C(6)**H**), 7.61 (ddd, *J* = 8.6, 7.3, 1.6, 1H, C(8)**H**), 7.54 – 7.42 (m, 2H, C(13)**H** & C(15)**H**), 7.41 – 7.29 (m, 3H, C(7)**H**, C(9)**H** & C(14)**H**), 7.22 – 7.12 (m, 2H, C(12)**H** & C(16)**H**), 5.41 (s, 1H, C(3)**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4 (q**C**-4), 162.6 (q**C**-2), 153.7 (q**C**-10), 152.5 (q**C**-11), 132.8 (**C**(8)H), 130.4 ((**C**(13)H) & (**C**(15)H)), 126.8 (**C**(14)H), 124.1 (**C**(7)H), 123.1 (**C**(6)H), 121.3 ((**C**(12)H) & (**C**(16)H)), 116.9 (**C**(9)H), 115.4 (q**C**-5), 93.6 (**C**(3)H); *m/z* (ES+): 239 ((M+H)$^+$ 96%).

Spectral characteristics were consistent with previously reported data.[31]

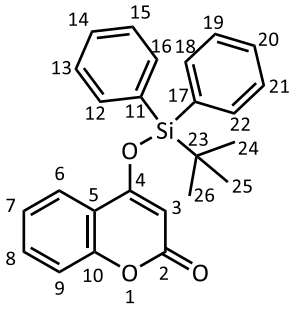
4-(Benzyloxy)-2*H*-chromen-2-one (98)



Compound **98** was prepared *via* the procedure described for compound **4** using 4-hydroxy-2*H*-chromen-2-one **19** (0.5 g, 3.08 mmol, 1.0 equiv.) and benzyl bromide (0.4 mL, 3.70 mmol, 1.2 equiv.). The residue was purified by column chromatography (DCM) to give a **98** as white solid (0.151 g, 19%); m.p. 164–167 °C; IR ν_{max} (film) 1728 (ester C=O stretch), 1627 (alkene C=C stretch), 1372 (ester C–O

stretch), 1251 (ether C–O stretch), 935 (alkene C–H bend), 742 (C–I stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.0, 1.4, 1H, ArC**H**), 7.62 – 7.50 (m, 1H, ArC**H**), 7.49 – 7.21 (m, 7H, 7 × ArC**H**), 5.78 (s, 1H, C(3)**H**), 5.20 (s, 2H, C(11)$\mathbf{H}_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3 (q**C**-4), 162.8 (q**C**-2), 153.4 (q**C**-10), 134.4 (q**C**-12), 132.5 (**C**(8)H), 128.9 (**C**(14)H & **C**(16)H), 128.9 (**C**(15)H), 127.8 (**C**(13)H & **C**(17)H), 123.9 (**C**(7)H), 123.2 (**C**(6)H), 116.8 (**C**(9)H), 115.7 (q**C**-5), 91.2 (**C**(3)H), 71.2 (**C**(11)H_2); *m/z* (ES+): 253 ([M+H]$^+$ 94%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{16}H_{13}O_3$ 253.0865, found 253.0857.

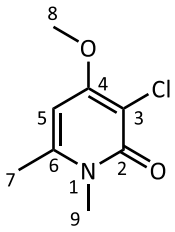
4-((*tert*-Butyldiphenylsilyl)oxy)-2*H*-chromen-2-one (100)



A Schlenk tube was heated under vacuum and refilled with N_2 three times, then allowed to cool to ambient temperature. Freshly distilled DCM (9 mL) and *tert*-butylchlorodiphenylsilane (TBDPSCl) (1.0 mL, 3.70 mmol, 1.2 equiv.) were added to the Schlenk tube, and the stirring solution was cooled to 0 °C using an ice-water bath. Et_3N (0.5 mL, 3.70 mmol, 1.2 equiv.), 4-hydroxy-2*H*-chromen-2-one **19** (0.5 g, 3.08 mmol, 1.0 equiv.), then DMAP (38 mg, 0.31 mmol, 0.1 equiv.) were added to the stirring solution. The Schlenk was removed from the ice-water bath and the solution was stirred at ambient temperature overnight (20 h). The solution was diluted with DCM (10 mL) and washed with brine (15 mL). The organic layer was dried, filtered and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (EtOAc:hexanes 10:90), and then recrystallised from EtOH to give a **100** as white solid (0.6697 g, 54%); m.p. 150–152 °C; IR ν_{max} (film) 1726 (ester C=O stretch), 1619 (alkene C=C stretch), 1387 (ester C–O stretch), 1238 (ether C–O stretch), 884 (alkene C–H bend); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 7.9, 1.6, 1H, ArC**H**), 7.77 – 7.67 (m, 4H, 4 × ArC**H**), 7.58 (ddd, *J* = 8.3, 7.4, 1.6, 1H, ArC**H**), 7.53 – 7.28 (m, 8H, 8 × ArC**H**), 5.29 (s, 1H, C(3)**H**), 1.18 (s, 9H, C(24)$\mathbf{H}_3$, C(25)$\mathbf{H}_3$ & C(26)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4 (q**C**-4), 162.7 (q**C**-2), 153.9 (q**C**-10), 135.2 (4 × Ar**C**H), 132.4 (Ar**C**H), 130.9 (2 × Ar**C**H), 129.9 (q**C**-11 & q**C**-17), 128.4 (4 × Ar**C**H), 124.0 (Ar**C**H), 123.3 (Ar**C**H), 117.7 (q**C**-5), 116.9 (Ar**C**H), 98.7 (**C**(3)H), 26.4 (**C**(24)H_3,

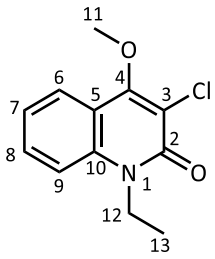
C(25)H_3 & **C**(26)H_3), 19.7 (q**C**-23); *m/z* (ES+): 401 ([M+H]$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{25}H_{25}O_3Si$ 401.1573, found 401.1555.

3-Chloro-4-methoxy-1,6-dimethylpyridin-2(1*H*)-one (101)



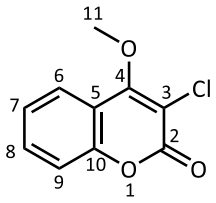
Compound **101** was prepared *via* the procedure described for compound **47** using 4-methoxy-1,6-dimethylpyridin-2(1*H*)-one **92** (1.2 g, 7.83 mmol, 1.0 equiv.), except that the mixture was stirred at 55 °C for 19 h. The residue was subjected to column chromatography (DCM) and further purified by recrystallisation from EtOH to yield **101** as a white solid (0.4452 g, 30%); m.p. 180–182 °C; IR ν_{max} (film) 1647 (C=O stretch), 1589 (alkene C=C stretch), 1535 (aromatic C–C stretch), 1083 (C–N stretch), 751 (C–Cl stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (s, 1H, C(5)**H**), 3.92 (s, 3H, C(8)**H**$_3$), 3.54 (s, 3H, C(9)**H**$_3$), 2.38 (s, 3H, C(7)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7 (q**C**-4), 160.7 (q**C**-2), 145.3 (q**C**-6), 105.2 (q**C**-3), 94.7 (**C**(5)H), 56.4 (**C**(8)H_3), 31.9 (**C**(9)H_3), 21.4 (**C**(7)H_3); *m/z* (ES+): 188 (^{35}Cl (M+H)$^+$ 78%), 190 (^{37}Cl (M+H)$^+$ 26%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_8H_{11}NO_2Cl$ 188.0478; Found 188.0480.

3-Chloro-1-ethyl-4-methoxyquinolin-2(1*H*)-one (103)



Compound **103** was prepared *via* the procedure described for compound **47** using 1-ethyl-4-methoxyquinolin-2(1*H*)-one **94** (1.3 g, 6.40 mmol, 1.0 equiv.), except that the mixture was stirred at 55 °C for 19 h. The residue was purified by column chromatography (EtOAc:hexanes 50:50) to yield **103** as a yellow solid (1.033 g, 68%); m.p. 73–76 °C; IR ν_{max} (film) 1652 (C=O stretch), 1615 (alkene C=C stretch), 1598 (aromatic C–C stretch), 1113 (C–N stretch), 755 (C–Cl stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.0, 1.4, 1H, C(6)**H**), 7.60 (ddd, *J* = 8.7, 7.2, 1.6, 1H, C(8)**H**), 7.40 (d, *J* = 8.5, 1H, C(9)**H**), 7.33 – 7.22 (m, 1H, C(7)**H**), 4.40 (q, *J* = 7.1, 2H, C(12)**H**$_2$), 4.12 (s, 3H, C(11)**H**$_3$), 1.37 (t, *J* = 7.1, 3H, C(13)**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7 (q**C**-4), 159.4 (q**C**-2), 137.1 (q**C**-10), 131.3 (**C**(8)H), 123.8 (**C**(7)H), 122.4 (**C**(6)H), 117.8 (q**C**-5), 115.0 (q**C**-3), 114.2 (**C**(9)H), 61.1 (**C**(11)H_3), 38.6 (**C**(12)H_2), 12.7 (**C**(13)H_3); *m/z* (ES+): 238 (^{35}Cl (M+H)$^+$ 14%), 240(^{37}Cl (M+H)$^+$ 6%); HRMS (ESI-TOF) *m/z*: [M+H]+ Calcd for $C_{12}H_{13}O_2NCl$ 238.0635; Found 238.0632.

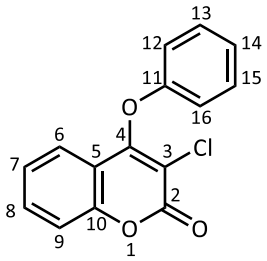
3-Chloro-4-methoxy-2*H*-chromen-2-one (104)[32]



Compound **104** was prepared using the procedure described for compound **107** using 4-methoxy-2*H*-chromen-2-one **91** (2.0 g, 11.35 mmol, 1.0 equiv.), except that the mixture was stirred at 85 °C for 1 h. The residues were recrystallised from EtOH to yield **104** as a cream solid (1.377 g, 58%); m.p. 84–85 °C (lit.[33] 87.9–88.6 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 – 7.75 (m, 1H, C(6)**H**), 7.63 – 7.51 (m, 1H, C(8)**H**), 7.38 – 7.28 (m, 2H, C(7)**H** & C(9)**H**), 4.34 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1 (q**C**-4), 159.6 (q**C**-2), 151.2 (q**C**-10), 132.4 (Ar**C**H), 124.6 (Ar**C**H), 123.4 (Ar**C**H), 117.2 (q**C**-5), 116.7 (Ar**C**H), 106.0 (q**C**-3), 61.6 (**C**(11)H$_3$); *m/z* (ES+): 211 (^{35}Cl (M+H)$^+$ 100%), 213 (^{37}Cl (M+H)$^+$ 32%).

Spectral characteristics were consistent with previously reported data.[32]

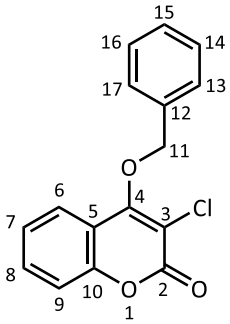
3-Chloro-4-phenoxy-2*H*-chromen-2-one (105)[31]



Compound **105** was prepared using the procedure described for compound **107** using 4-phenoxy-2*H*-chromen-2-one **97** (1.0 g, 4.20 mmol, 1.0 equiv.), except that the mixture was stirred at 85 °C for 1 h. The residues were triturated in EtOH to yield **105** as a pale orange solid (0.727 g, 64%); m.p. 70–75 °C (lit.[31] 74–75 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.53 (m, 2H, 2 × Ar**C**H), 7.47 – 7.24 (m, 4H, 4 × Ar**C**H), 7.14 (t, *J* = 7.4, 1H, Ar**C**H), 7.05 – 6.94 (m, 2H, 2 × Ar**C**H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8 (q**C**-4), 158.4 (q**C**-2), 155.6 (q**C**-10), 151.7 (q**C**-11), 132.8 (Ar**C**H), 130.1 (2 × Ar**C**H), 125.0 (Ar**C**H), 124.1 (Ar**C**H), 123.8 (Ar**C**H), 117.0 (Ar**C**H), 116.7 (q**C**-5), 116.1 (2 × Ar**C**H), 112.0 (q**C**-3); *m/z* (ES+): 273 (^{35}Cl (M+H)$^+$ 58%), 275 (^{37}Cl (M+H)$^+$ 18%).

Spectral characteristics were consistent with previously reported data.[31]

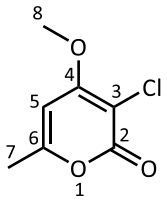
4-(Benzyloxy)-3-chloro-2*H*-chromen-2-one (106)[34]



Compound **106** was prepared using the procedure described for compound **107** using 4-benzyloxy-2*H*-chromen-2-one **98** (0.19 g, 0.737 mmol, 1.0 equiv.), except that the mixture was stirred at 85 °C for 1 h. The residues were purified by column chromatography (DCM) to yield **106** as a white solid (0.142 g, 67%); m.p. 88–90 °C (lit.[34] 68 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 – 7.66 (m, 1H, ArC**H**), 7.54 (ddd, *J* = 8.4, 7.3, 1.6, 1H, ArC**H**), 7.50 – 7.35 (m, 5H, 5 × ArC**H**), 7.35 – 7.22 (m, 2H, 2 × ArC**H**), 5.55 (s, 2H, C(11)**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6 (q**C**-4), 159.4 (q**C**-2), 151.3 (q**C**-10), 135.2 (q**C**-12), 132.5 (**C**(8)H), 129.1 (**C**(15)H), 128.9 (**C**(14)H & **C**(16)H), 128.4 (**C**(13)H & **C**(17)H), 124.7 (**C**(7)H), 123.7 (**C**(6)H), 117.6 (q**C**-5), 116.6 (**C**(9)H), 107.3 (q**C**-3), 75.9 (**C**(11)H$_2$); *m/z* (ES+): 287 (^{35}Cl (M+H)$^+$ 100%), 289 (^{37}Cl (M+H)$^+$ 34%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{16}H_{12}O_3Cl$ 287.0475; Found 287.0465.

Spectral characteristics were consistent with previously reported data.[34]

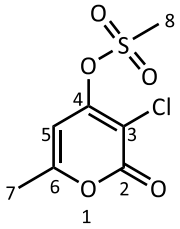
3-Chloro-4-methoxy-6-methyl-2*H*-pyran-2-one (107)



To a 100 mL round-bottomed flask were added 4-methoxy-6-methyl-2*H*-pyran-2-one **90** (2.17 g, 15.48 mmol, 1.0 equiv.) and trichloroisocyanuric acid (TCCA) (1.80 g, 7.74 mmol, 0.5 equiv.). EtOAc (50 mL) was slowly added to the mixture. The flask was placed in an oil bath, which was then heated to 85 °C. The mixture was stirred at this temperature for 4 h, then cooled to ambient temperature. The reaction mixture was filtered through fluted filter paper to remove the insoluble material, and the filtrate was concentrated under reduced pressure. The residues were recrystallised from EtOH to yield **107** as a yellow solid (1.5342 g, 57%); m.p. 140–142 °C (lit.[35] 147–148 °C); IR ν_{max} (film) 1704 (ester C=O stretch), 1537 (alkene C=C stretch), 1322 (ester C–O stretch), 1233 (ether C–O stretch), 737 (C–Cl stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (d, *J* = 0.6, 1H, C(5)**H**), 4.00 (s, 3H, C(8)**H**$_3$), 2.31 (d, *J* = 0.7, 3H, C(7)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2 (q**C**-4), 161.9 (q**C**-2), 160.9 (q**C**-6), 99.3 (q**C**-3), 95.2 (**C**(5)H), 57.3 (**C**(8)H_3), 20.3 (**C**(7)H_3); *m/z* (ES+): 175 (^{35}Cl (M+H)$^+$ 100%), 177 (^{37}Cl (M+H)$^+$ 40%);

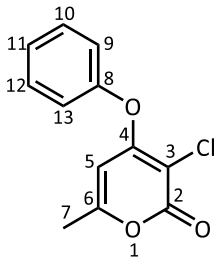
HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_7H_8ClO_3$ 175.0162; Found 175.0154; Anal. Calc. for $C_7H_7ClO_3$: C, 48.16; H, 4.04; Found: C, 48.27; H, 4.08.

3-Chloro-6-methyl-2-oxo-2*H*-pyran-4-yl methanesulfonate (108)



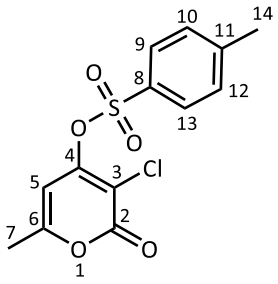
Compound **108** was prepared using the procedure described for compound **107** using 6-methyl-2-oxo-2*H*-pyran-4-yl methanesulfonate **95** (2.0 g, 9.79 mmol, 1.0 equiv.), except that the mixture was stirred at 85 °C for 24 h. The filtrate was concentrated under reduced pressure to give a viscous yellow oil, which was crystallised from EtOH to give **108** as an off-white solid (0.7359 g, 31%); m.p. 107–110 °C; IR ν_{max} (film) 1738 (ester C=O stretch), 1642 (alkene C=C stretch), 1556 (aromatic C–C stretch), 1376 (ester C–O stretch), 1189 (ether C–O stretch), 790 (C–Cl stretch); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (d, *J* = 0.7, 1H, C(5)**H**), 3.37 (d, *J* = 0.5, 1H, C(8)**H**$_3$), 2.32 (d, *J* = 0.6, 1H, C(7)**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4 (q**C**-4), 159.7 (q**C**-6), 156.2 (q**C**-2), 109.6 (q**C**-3), 101.7 (**C**(5)H), 40.1 (**C**(8)H$_3$), 20.0 (**C**(7)H$_3$); *m/z* (ES+): 239 (^{35}Cl $(M+H)^+$ 50%), 241 (^{37}Cl $(M+H)^+$ 26%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_7H_8O_5SCl$ 238.9781; Found 238.9787.

3-Chloro-4-phenoxy-6-methyl-2*H*-pyran-2-one (109)



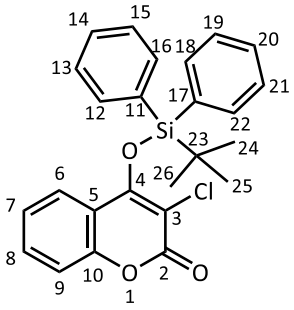
Compound **109** was prepared using the procedure described for compound **107** using 4-phenoxy-6-methyl-2*H*-pyran-2-one (161 mg, 0.80 mmol, 1.0 equiv.), except that the mixture was stirred at 85 °C for 6 h. The residue was purified by column chromatography (EtOAc:hexanes 25:75) to yield **109** as a pale yellow solid (0.078 g, 27%); m.p. 100–103 °C (lit.[31] 96–97 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.41 (m, 2H, C(10)**H** & C(12)**H**), 7.40 – 7.26 (m, 1H, C(11)**H**), 7.16 – 7.04 (m, 2H, C(9)**H** & C(13)**H**), 5.68 (s, 1H, C(5)**H**), 2.19 (s, 3H, C(7)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6 (q**C**-4), 161.4 (q**C**-2), 160.9 (q**C**-8), 152.8 (q**C**-6), 130.4 (**C**(10)H & **C**(12)H), 126.5 (**C**(11)H), 120.8 (**C**(9)H & **C**(13)H), 101.7 (q**C**-3), 97.6 (**C**(5)H), 20.1 (**C**(7)H$_3$); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{10}ClO_3$ 237.0318; Found 237.0312.

3-Chloro-6-methyl-2-oxo-2*H*-pyran-4-yl 4-methylbenzenesulfonate (110)



Compound **110** was prepared using the procedure described for compound **107** using 6-methyl-2-oxo-2*H*-pyran-4-yl 4-methylbenzenesulfonate **80** (1.5 g, 5.35 mmol, 1.0 equiv.), except that the mixture was stirred at 85 °C for 24 h. The residues were recrystallised from EtOH to yield **110** as a pale yellow solid (0.6730 g, 40%); m.p. 144–147 °C; IR ν_{max} (film) 1741 (ester C=O stretch), 1547 (alkene C=C stretch), 1386 (ester C–O stretch), 1195 (ether C–O stretch), 666 (C–Cl stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4, 2H, C(9)**H** & C(13)**H**), 7.39 (d, *J* = 8.1, 2H, C(10)**H** & C(12)**H**), 6.43 (d, *J* = 0.8, 1H, C(5)**H**), 2.48 (s, 3H, C(14)$\mathbf{H}_3$), 2.30 (d, *J* = 0.7, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0 (q**C**-4), 159.8 (q**C**-2), 156.5 (q**C**-6), 147.0 (q**C**-8), 131.9 (q**C**-11), 130.3 (**C**(10)H & **C**(12)H), 128.5 (**C**(9)H & **C**(13)H), 110.0 (q**C**-3), 101.6 (**C**(5)H), 21.9 (**C**(14)H_3), 19.9 (**C**(7)H_3); *m/z* (ES+): 315 (^{35}Cl (M+H)$^+$ 100%), 317 (^{37}Cl (M+H)$^+$ 40%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{13}H_{12}ClSO_5$ 315.0094; Found 315.0086.

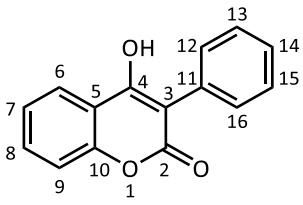
4-((*tert*-Butyldiphenylsilyl)oxy)-3-chloro-2*H*-chromen-2-one (141)



Compound **141** was prepared using the procedure described for compound **107** using 4-((*tert*-butyldiphenylsilyl)oxy)-2*H*-chromen-2-one **100** (200 mg, 0.50 mmol, 1.0 equiv.), except that the mixture was stirred at 85 °C for 2 h. The residues were purified by column chromatography (DCM) to yield **141** as a colourless oil (0.027 g, 12%); IR ν_{max} (film) 1709 (C=O stretch), 1606 (alkene C=C stretch), 1555 (aromatic C–C stretch), 1365 (C–O stretch), 700 (C–Cl stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 – 7.69 (m, 5H, 5 × ArC**H**), 7.56 – 7.30 (m, 8H, 8 × ArC**H**), 7.18 (ddd, *J* = 8.3, 7.3, 1.1, 1H, ArC**H**), 1.18 (s, 9H, C(24)**H**, C(25)**H** & C(26)**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5 (q**C**-4), 158.6 (q**C**-2), 151.3 (q**C**-10), 134.8 (4 × Ar**C**H), 132.1 (Ar**C**H), 131.8 (2 × q**C**-Ar), 130.5 (2 × Ar**C**H), 128.0 (4 × Ar**C**H), 124.2 (Ar**C**H), 124.0 (Ar**C**H), 117.7 (q**C**-5), 116.9 (Ar**C**H), 106.4 (q**C**-3), 26.6 (**C**(24)H, **C**(25)H & **C**(26)H), 20.5 (q**C**-23); *m/z* (ES+): 435 (^{35}Cl (M+H)$^+$ 100%), 437 (^{37}Cl

$(M+H)^+$ 58%); HRMS (ESI-TOF) *m/z*: [M+H]+ Calcd for $C_{25}H_{24}O_3SiCl$ 435.1183; Found 435.1190.

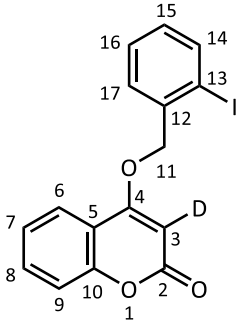
4-Hydroxy-3-phenyl-2*H*-chromen-2-one (143)[36]



To an oven-dried reaction tube were added NaI (120 mg, 0.792 mmol, 4.0 equiv.) and CH_3CN (1 mL, stored over 4 Å molecular sieves before use), and the mixture was stirred at ambient temperature. To the stirring mixture was added TMSCl (0.05 mL, 0.396 mmol, 2.0 equiv.). The mixture was stirred at ambient temperature for 1 h. 4-Methoxy-3-phenyl-2*H*-chromen-2-one **111** (50 mg, 0.198 mmol, 1.0 equiv.) was added to the stirring mixture. The mixture was stirred at 25 °C overnight with the reaction tube open to the air, then poured into a beaker containing cold 1 M aqueous HCl (15 mL). The mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with 5% aqueous sodium thiosulfate (25 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc:hexanes 20:80 → 50:50) to yield **143** as a pale pink solid (0.024 g, 51%); m.p. 232–233 °C (lit.[37] 232–233 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.02 (dd, *J* = 7.9, 1.2, 1H, C(6)**H**), 7.72 – 7.61 (m, 1H, C(8)**H**), 7.49 – 7.31 (m, 7H, 7 × ArC**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.4 (q**C**-4), 160.7 (q**C**-2), 152.8 (q**C**-10), 132.8 (**C**(14)H), 132.5 (q**C**-11), 131.5 (**C**(12)H & **C**(16)H), 128.5 (**C**(13)H & **C**(15)H), 127.9 (**C**(8)H), 124.4 **C**(7)H, 124.2 (**C**(6)H), 116.9 (q**C**-5), 116.7 (**C**(9)H), 106.6 (q**C**-3); *m/z* (ES−): 237 ($(M-H)^-$ 100%).

Spectral characteristics were consistent with previously reported data.[36]

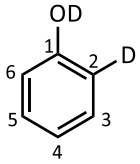
4-((2-Iodobenzyl)oxy)-*2H*-chromen-2-one-3-d (148)



4-Hydroxy-2*H*-chromen-2-one **19** (200 mg, 1.233 mmol, 1.0 equiv.), D_2O (0.5 mL) and acetone-d_6 (1 mL) were added to a 2-5 mL Smith MW vial and the reaction mixture was irradiated (300 W) with stirring for 1.5 h at 140 °C. The reaction mixture was allowed cool to room temperature. 2-Iodobenzyl bromide **2** (440 mg, 1.480 mmol, 1.2 equiv.) and K_2CO_3 (511 mg, 3.70 mmol,

3.0 equiv.) were added. The reaction mixture was irradiated (300 W) with stirring for 30 min at 100 °C. The reaction mixture was allowed cool to room temperature. DCM (5 mL) and D_2O (5 mL) were added. The layers were separated and the aqueous layer was washed with DCM (2 × 5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resiude was purified by column chromatography (DCM) to give **148** as a white solid (203 mg, 43%, 98% D); m.p. 159–161 °C; IR ν_{max} (film) 1708 (ester C=O stretch), 1605 (alkene C=C stretch), 1557 (aromatic C–C stretch), 1348 (ester C–O stretch), 1158 (ether C–O stretch), 965 (alkene C–D bend), 761 (C–I stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 – 7.86 (m, 2H, C(14)**H** & C(16)**H**), 7.63 – 7.53 (m, 1H, C(17)**H**), 7.53 – 7.39 (m, 2H, C(6)**H** & C(8)**H**), 7.38 – 7.28 (m, 2H, C(7)**H** & C(9)**H**), 7.12 (td, *J* = 7.6, 1.8, 1H, C(15)**H**), 5.81 (s, 0.02H, C(3)**H**), 5.20 (s, 2H, C(11)$\mathbf{H}_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0 (q**C**-4), 162.8 (q**C**-2), 153.4 (q**C**-10), 139.8 (**C**(14)H), 136.7 (q**C**-12), 132.6 (**C**(15)H), 130.5 (**C**(17)H), 129.1 (**C**(8)H), 128.6 (**C**(16)H), 124.0 (**C**(7)H), 123.2 (**C**(6)H), 116.9 (**C**(9)H), 115.6 (q**C**-5), 97.9 (q**C**-13), 91.5 (t, *J* = 26, q**C**-3), 74.8 (**C**(11)H_2); *m/z* (ES+): 380 ($(M+H)^+$ 98%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{11}DO_3I$ 379.9894; Found 379.9909.

2-Deuteriophenol (150)[38]

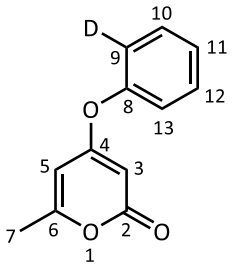


A 2-neck, 100 mL round-bottomed flask was heated under vacuum and refilled with N_2 three times. Freshly distilled THF (35 mL) was added, followed by 2-bromophenol (2.0 mL, 17.3 mmol, 1 equiv.). The solution was cooled to 0 °C with stirring. *n*BuLi (13.9 mL, 2.5 M in hexanes) was added steadily over 15 min. The reaction mixture was stirred at 0°C for 3 hours and quenched with D_2O (4.0 mL, 221 mmol, 12.8 equiv.) over 10 min. The reaction was maintained at 0 °C for a further 5 min, then stirred at ambient temperature for 1 h. The reaction mixture was then concentrated under reduced pressure. The residue was dissolved in Et_2O (50 mL) and then washed with saturated aqueous NH_4Cl (2 × 25 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by column chromatography (EtOAc:hexanes 5:95) to yield **150** as a pale yellow oil (1.025 g, 62%, 80% D); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.16 (m, 2H, C(3)**H** & C(5)**H**), 6.93 (td, *J* = 7.4, 1.0, 1H, C(4)**H**), 6.87 – 6.78 (m, 1.2H, C(2)**H**

& C(6)**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4 (q**C**-1), 129.7 (**C**(3)H & **C**(5)H), 120.8 (**C**(4)H), 115.4 (q**C**-2 & **C**(6)H); *m/z* (ES-): 95 ($(M-H)^-$ 8%).

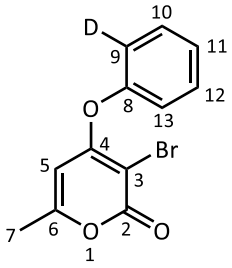
Spectral characteristics were consistent with previously reported data.[39]

4-(2-Deuteriophenoxy)-6-methyl-2*H*-pyran-2-one (151)



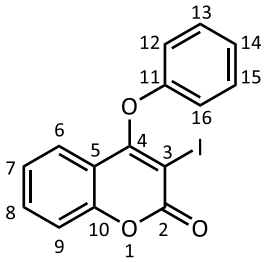
Compound **151** was prepared *via* the procedure described for compound **97** using 4-bromo-6-methyl-2*H*-pyran-2-one **6** (1.48 g, 7.80 mmol, 1.0 equiv.) and 2-deuteriophenol **150** (0.9 g, 9.36 mmol, 1.2 equiv.) to yield **151** as a dark orange solid (1.403 g, 88%, 80% D) which did not require further purification; m.p. 76–81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.49 – 7.38 (m, 2H, C(10)**H** & C(12)**H**), 7.34 – 7.25 (m, 1H, C(11)**H**), 7.11 – 7.03 (m, 1.2H, C(9)**H** & C(13)**H**), 6.00 – 5.95 (m, 1H, C(5)**H**), 5.20 (d, *J* = 2.1, 1H, C(3)**H**), 2.26 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8 (q**C**-4), 164.7 (q**C**-2), 163.3 (q**C**-6), 152.3 (q**C**-8), 130.2 (**C**(10)H & **C**(12)H), 126.6 (**C**(11)H), 121.1 (q**C**-9 & **C**(13)H), 100.0 (**C**(5)H), 91.0 (**C**(3)H), 20.1 (**C**(7)H_3); *m/z* (ES+): 204 ($(M+H)^+$ 32%).

3-Bromo-4-(2-deuteriophenoxy)-6-methyl-2*H*-pyran-2-one (152)

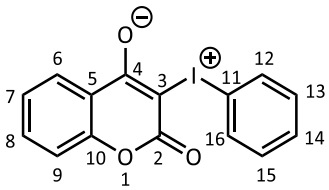


To a stirring solution of 4-(2-deuteriophenoxy)-6-methyl-2*H*-pyran-2-one **151** (0.6 g, 2.95 mmol, 1.0 equiv.) in DCM (10 mL) was added Br_2 (0.2 mL, 3.25 mmol, 1.1 equiv.). The round-bottomed flask was wrapped in aluminium foil to exclude light. The reaction was stirred at ambient temperature for 3 h, then concentrated under reduced pressure. The crude residue was recrystallised from EtOH to yield **152** as a pale yellow solid (0.5209 g, 74%, 80% D); m.p. 118–120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 – 7.39 (m, 2H, C(10)**H** & C(12)**H**), 7.39 – 7.28 (m, 1H, C(11)**H**), 7.10 (dd, *J* = 8.5, 1.0, 1.2H, C(9)**H** & C(13)**H**), 5.62 (d, *J* = 0.8, 1H, C(5)**H**), 2.16 (d, *J* = 0.8, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6 (q**C**-4), 162.3 (q**C**-2), 160.9 (q**C**-6), 152.8 (q**C**-8), 130.3 (**C**(10)H & **C**(12)H), 126.6 (**C**(11)H), 120.6 (q**C**-9 & **C**(13)H), 97.6 (**C**(5)H), 90.9 (q**C**-3), 20.1 (**C**(7)H_3); *m/z* (ES+): 282 (^{79}Br $(M+H)^+$ 68%), 284 (^{81}Br $(M+H)^+$ 67%).

3-Iodo-4-phenoxy-2*H*-chromen-2-one (155)[40]



A solution of Na_2CO_3 (1.1 g, 10.0 mmol, 1.0 equiv.) in H_2O (100 mL) was prepared in a 250 mL round-bottomed flask. Phenyliodo(III)diacetate (PIDA) (3.2 g, 10.0 mmol, 1.0 equiv.) was added and the mixture was stirred at ambient temperature for 30 min. In a 500 mL round-bottomed flask, 4-hydroxy-2*H*-chromen-2-one **19** (1.6 g, 10.0 mmol, 1.0 equiv.) and Na_2CO_3 (1.1 g, 10.0 mmol, 1.0 equiv.) in H_2O (100 mL) were stirred to give a solution. The PIDA mixture was added to the coumarin solution. The reaction mixture was stirred at ambient temperature for 2 h. The solid was isolated by suction filtration, washed with H_2O and triturated in MeOH to give 2-oxo-3-(phenyliodonio)-2*H*-chromen-4-olate[41] as an off-white solid (2.1012 g, 58%).



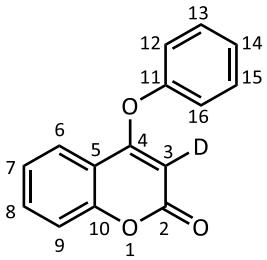
m.p. 147–152 °C (lit.[41] 136 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.95 – 7.82 (m, 3H, 3 × ArC**H**), 7.62 – 7.48 (m, 2H, 2 × ArC**H**), 7.47 – 7.36 (m, 2H, 2 × ArC**H**), 7.33 – 7.19 (m, 2H, 2 × ArC**H**); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.6 (q**C**-Ar), 161.0 (q**C**-Ar), 153.9 (q**C**-Ar), 133.1 (2 × Ar**C**H), 132.9 (Ar**C**H), 131.1 (2 × Ar**C**H), 130.7 (Ar**C**H), 125.7 (Ar**C**H), 123.5 (Ar**C**H), 119.9 (q**C**), 116.3 (Ar**C**H), 115.0 (q**C**), 82.0 (q**C**-3); *m/z* (ES+) 365 ((M+H)$^+$ 18%); Anal. Calc. for $C_{15}H_9IO_3$: C, 49.48; H, 2.49; Found: C, 49.06; H, 2.45.

A solution of 2-oxo-3-(phenyliodonio)-2*H*-chromen-4-olate (1.9 g, 5.22 mmol, 1.0 equiv.) in anhydrous DMF (20 mL) was prepared in a 50 mL round-bottomed flask. A condenser was fitted to the flask and the flask was placed in a sand bath preheated to 165 °C. The mixture was stirred at this temperature for 15 min, during which time the mixture changed from yellow to orange. The flask was cooled to ambient temperature. The mixture was concentrated under reduced pressure and the residue was transferred to a conical flask. H_2O (40 mL) was added and a yellow precipitate formed. The precipitate was isolated by suction filtration and recrystallised from MeOH to give **155** as a yellow crystalline solid (1.2621 g, 66%); m.p. 134–136 °C (lit.[41] 138–139 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 – 7.50 (m, 2H, 2 × ArC**H**), 7.43 (dd, *J* =

8.3, 0.6, 1H, ArC**H**), 7.39 – 7.30 (m, 2H, 2 × ArC**H**), 7.25 – 7.08 (m, 2H, 2 × ArC**H**), 7.02 – 6.88 (m, 2H, 2 × ArC**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0 (q**C**-4), 159.6 (q**C**-2), 155.5 (q**C**-11), 153.4 (q**C**-10), 133.1 (**C**(8)H), 130.2 (**C**(13)H & **C**(15)H), 124.7 (**C**(7)H), 123.9 (**C**(6)H), 123.8 (**C**(14)H), 116.9 (**C**(9)H), 116.3 (q**C**-5), 116.0 (**C**(12)H & **C**(16)H), 80.5 (q**C**-3); *m/z* (ES+) 365 ((M+H)$^+$ 100%); Anal. Calc. for $C_{15}H_9IO_3$: C, 49.48; H, 2.49; Found: C, 49.44; H, 2.52.

Spectral characteristics were consistent with previously reported data.[40]

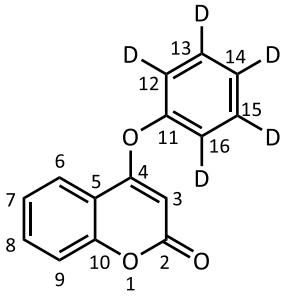
3-Deuterio-4-phenoxy-2*H*-chromen-2-one (156)



A Schlenk tube was heated under vacuum and refilled with N_2 three times. 3-Iodo-4-phenoxy-2*H*-chromen-2-one **155** (1.20 g, 3.30 mmol, 1.0 equiv.) and zinc dust (1.1 g, 20.60 mmol, 6.2 equiv.) were added to the Schlenk tube. The Schlenk tube was evacuated and refilled with N_2 three times. Monodeuterioacetic acid (AcOD) (10 mL) was added and the mixture was stirred at ambient temperature for 17 h. A saturated solution of K_2CO_3 in D_2O (2 mL) was slowly added, evolving gas and forming a precipitate. The mixture was stirred at ambient temperature for 30 min. The mixture was diluted with DCM (25 mL), dissolving the precipitate, and the zinc metal was removed by gravity filtration. The layers in the filtrate were separated and the aqueous layer was washed with DCM (2 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude yellow residue was purified by column chromatography (DCM) to yield **156** as a pale yellow solid (0.680 g, 86%, 97% D); m.p. 134–135 °C; IR ν_{max} (film); 1726 (ester C=O stretch), 1619 (alkene C=C stretch), 1368 (ester C–O stretch), 1190 (ether C–O stretch), 752 (alkene C-H bend); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.3, 1.5, 1H, C(9)**H**), 7.67 – 7.56 (m, 1H, C(7)**H**), 7.54 – 7.42 (m, 2H, C(13)**H** & C(15)**H**), 7.42 – 7.29 (m, 3H, C(6)**H**, C(8)**H** & C(14)**H**), 7.18 (dd, *J* = 7.5, 1.1, 2H, C(12)**H** & C(16)**H**), 5.41 (s, 0.03H, C(3)**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3 (q**C**-4), 162.5 (q**C**-2), 153.7 (q**C**-11), 152.5 (q**C**-10), 132.8 (**C**(7)H), 130.4 (**C**(13)H & **C**(15)H), 126.8 (**C**(8)H), 124.1 (**C**(14)H), 123.1 (**C**(9)H), 121.3 (**C**(12)H & **C**(16)H), 116.8 (**C**(6)H), 115.4 (q**C**-5), 93.3 (t, *J* = 25, q**C**-3); *m/z* (ES+): 240 ((M+H)$^+$ 74%); HRMS (ESI-TOF) *m/z*:

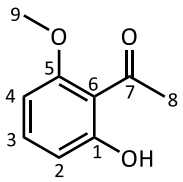
[M+H]$^+$ Calcd for $C_{15}H_{10}DO_3$ 240.0771; Found 240.0771; Anal. Calcd. for $C_{15}H_9DO_3$: C, 75.30; H, 4.63; Found: C, 75.10; H, 4.37.

4-(Phenoxy-d$_5$)-2*H*-chromen-2-one (157)



Compound **157** was prepared *via* the procedure described for compound **97** using 4-bromo-2*H*-chromen-2-one **96** (1.0 g, 4.44 mmol, 1.0 equiv.) and phenol-d$_6$ (0.5 g, 4.89 mmol, 1.1 equiv.) to yield **157** as a light brown solid (0.9282 g, 86%) which did not require further purification; m.p. 131–133 °C; IR ν_{max} (film) 1725 (ester C=O stretch), 1625 (alkene C=C stretch), 1568 (aromatic C–C stretch), 1371 (ester C–O stretch), 1224 (ether C–O stretch), 790 (alkene C–H bend); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 7.9, 1.2, 1H, C(9)**H**), 7.62 (ddd, *J* = 8.6, 7.3, 1.6, 1H, C(7)**H**), 7.42 – 7.29 (m, 2H, C(6)**H** & C(8)**H**), 5.42 (s, 1H, C(3)**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4 (q**C**-4), 162.6 (q**C**-2), 153.7 (q**C**-11), 152.4 (q**C**-10), 132.8 (**C**(7)H), 129.9 (t, *J* = 25, q**C**-13 & q**C**-15), 126.3 (t, *J* = 25, q**C**-14), 124.1 (**C**(8)H), 123.1 (**C**(9)H), 120.9 (t, *J* = 25, q**C**-12 & q**C**-16), 116.9 (**C**(6)H), 115.5 (q**C**-5), 93.6 (**C**(3)H); *m/z* (ES+): 244 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{15}H_6D_5O_3$ 244.1022; Found 244.1022.

2'-Hydroxy-6'-methoxyacetophenone (158)[42]

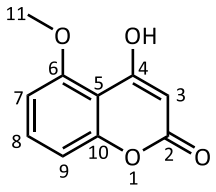


Following the literature procedure,[42] 2',6'-dihydroxyacetophenone (5.0 g, 32.86 mmol, 1.0 equiv.), K_2CO_3 (4.5 g, 32.86 mmol, 1.0 equiv.) and acetone (100 mL) were added to a 250 mL round-bottomed flask and the mixture was set stirring at ambient temperature. Methyl iodide (2 mL, 32.86 mmol, 1.0 equiv.) was added and the mixture was heated to 79 °C using an oil bath. The reaction was stirred at this temperature for 24 h, then cooled to ambient temperature. The mixture was filtered through fluted filter paper and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc:hexanes 20:80) to yield **158** as a yellow solid (4.0666 g, 74%); m.p. 53–56 °C (lit.[42] 57–58 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.24 (s, 1H, O–**H**), 7.33 (t, *J* = 8.4, 1H, C(3)**H**), 6.55 (dd, *J* = 8.4, 0.9, 1H, C(2)**H**), 6.38 (d, *J* = 8.3, 1H, C(4)**H**), 3.89 (s, 3H, C(9)**H**$_3$), 2.66 (s, 3H, C(8)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.2

(q**C**-7), 164.7 (q**C**-1), 161.5 (q**C**-5), 136.1 (**C**(3)H), 111.3 (q**C**-6), 110.7 (**C**(2)H), 101.1 (**C**(4)H), 55.6 (C(8)**H**$_3$), 33.7 (**C**(9)H$_3$); *m/z* (ES+): 167 ((M+H)$^+$ 100%).

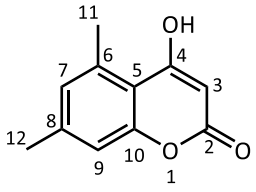
Spectral characteristics were consistent with previously reported data.[42]

4-Hydroxy-5-methoxy-2*H*-chromen-2-one (159)[43]



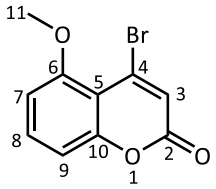
Modifying the literature procedures,[44-45] a 100 mL, 2-neck round-bottomed flask was heated under vacuum and refilled with N_2. 2'-Hydroxy-6'-methoxyacetophenone **158** (4.5 g, 27.08 mmol, 1.0 equiv.) and toluene (30 mL) were added. A 500 mL, 3-neck round-bottomed flask was heated under vacuum and refilled with N_2. NaH (11.8 g, 55% dispersion in mineral oil, 10.0 equiv.) and toluene (60 mL) were added. The acetophenone solution was added dropwise to the stirring suspension of NaH over 15 min. The mixture was stirred until hydrogen evolution ceased, about 10 min. A solution of diethyl carbonate (4.4 mL, 36.11 mmol, 1.5 equiv.) in toluene (10 mL) was added to the reaction mixture over 5 min. The reaction mixture was stirred at ambient temperature for 15 min., then heated to 110 °C using an oil bath. The reaction was stirred at this temperature for 21 h, then cooled to ambient temperature. The mixture was concentrated under reduced pressure to obtain a yellow solid which was slowly added to 100 mL of ice water. The mixture was acidified with aqueous HCl (36.5-38.5%) until no further precipitate was formed and the mixture was pH 2 as indicated by universal indicator paper. The precipitate was isolated by suction filtration, and washed with H_2O. The resulting solid was recrystallised from EtOH to yield **159** as a cream solid (1.2265 g, 24%); m.p. 153–154 °C (lit.[46] 152–153 °C); ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 11.32 (br s, 1H, O–**H**), 7.55 (t, *J* = 8.4, 1H, C(8)**H**), 7.10 – 6.66 (m, 2H, C(7)**H** & C(9)**H**), 5.51 (s, 1H, C(3)**H**), 3.90 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ 167.7 (q**C**-4), 161.9 (q**C**-2), 157.8 (q**C**-6), 155.6 (q**C**-10), 133.5 (**C**(8)H), 109.7 (**C**(9)H), 107.2 (**C**(7)H), 105.5 (q**C**-5), 91.3 (**C**(3)H), 57.0 (**C**(11)H$_3$); *m/z* (ES+) 193 ((M+H)$^+$ 100%).

4-Hydroxy-5,7-dimethyl-2*H*-chromen-2-one (160)[47]



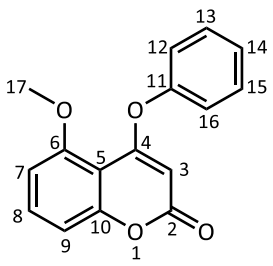
Compound **160** was prepared *via* the procedure described for compound **21** using 3,5-dimethylphenol (1.0 g, 8.19 mmol, 1.0 equiv.) to yield **160** as a pale yellow solid (1.2183 g, 78%); m.p. >250 °C (lit.[47] 219–220 °C); IR ν_{max} (film) 1644 (C=O stretch), 1604 (alkene C=C stretch), 1550 (aromatic C–C stretch), 1345 (C–O stretch), 1271 (C–O stretch); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.21 (s, 1H, O–**H**), 6.97 (d, *J* = 0.6, 1H, C(9)**H**), 6.89 (d, *J* = 0.7, 1H, C(7)**H**), 5.48 (s, 1H, C(3)**H**), 2.60 (s, 3H, C(12)**H**$_3$), 2.31 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.2 (q**C**-4), 162.1 (q**C**-2), 155.6 (q**C**-10), 142.7 (q**C**-8), 137.1 (q**C**-6), 128.7 (**C**(7)H), 115.2 (**C**(9)H), 112.2 (q**C**-5), 90.8 (**C**(3)H), 22.9 (**C**(12)H$_3$), 21.2 (**C**(11)H$_3$); *m/z* (ES+) 191 ((M+H)$^+$ 6%).

4-Bromo-5-methoxy-2*H*-chromen-2-one (161)



Compound **161** was prepared *via* the procedure described for compound **6** using 4-hydroxy-5-methoxy-2*H*-chromen-2-one **159** (0.77 g, 4.01 mmol, 1.0 equiv.) to yield **161** as a yellow solid (0.314 g, 31%) which did not require further purification; m.p. >250 °C; IR ν_{max} (film) 1651 (ester C=O stretch), 1072 (ester C–O stretch), 981 (alkene C–H bend), 666 (C–Br stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (t, *J* = 8.4, 1H, C(8)**H**), 6.92 (dd, *J* = 8.4, 0.8, 1H, C(7)**H**), 6.78 (d, *J* = 8.4, 1H, C(9)**H**), 6.74 (s, 1H, C(3)**H**), 3.93 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5 (q**C**-2), 157.0 (q**C**-6), 154.1 (q**C**-10), 136.5 (q**C**-4), 133.1 (**C**(8)H), 120.1 (**C**(9)H), 109.6 (**C**(7)H), 108.6 (q**C**-5), 107.1 (**C**(3)H), 56.0 (**C**(11)H$_3$); *m/z* (ES+): 255 (^{79}Br (M+H)$^+$ 100%), 257 (^{81}Br (M+H)$^+$ 98%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{10}H_8O_3Br$ 254.9657; Found 254.9646.

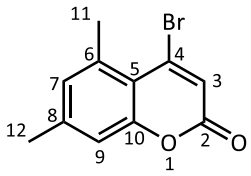
5-Methoxy-4-phenoxy-2*H*-chromen-2-one (162)



Compound **162** was prepared *via* the procedure described for compound **97** using 4-bromo-5-methoxy-2*H*-chromen-2-one **161** (0.15 g, 0.588 mmol, 1.0 equiv.) and phenol (0.06 g, 0.647 mmol, 1.1 equiv.). The residue was purified by column chromatography (EtOAc:hexanes 70:30) to yield **162** as an

off-white solid (0.020 g, 13%); m.p. 213–215 °C; IR ν_{max} (film) 1705 (ester C=O stretch), 1614 (aromatic C–C stretch), 1255 (ester C–O stretch), 1095 (ether C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.41 (m, 3H, 3 × ArC**H**), 7.36 – 7.27 (m, 1H, ArC**H**), 7.22 – 7.09 (m, 2H, 2 × ArC**H**), 6.98 (dd, *J* = 8.4, 0.9, 1H, ArC**H**), 6.81 (d, *J* = 8.4, 1H, ArC**H**), 5.33 (s, 1H, C(3)**H**), 3.93 (s, 3H, C(17)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7 (q**C**-4), 162.5 (q**C**-2), 158.0 (q**C**-6), 155.7 (q**C**-11), 152.8 (q**C**-10), 132.8 (Ar**C**H), 130.4 (2 × Ar**C**H), 126.4 (Ar**C**H), 121.4 (2 × Ar**C**H), 109.8 (Ar**C**H), 106.7 (Ar**C**H), 105.8 (q**C**-5), 93.4 (**C**(3)H), 56.5 (**C**(17)H_3); *m/z* (ES+): 269 ((M+H)$^+$ 58%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{16}H_{13}O_4$ 269.0814; Found 269.0814.

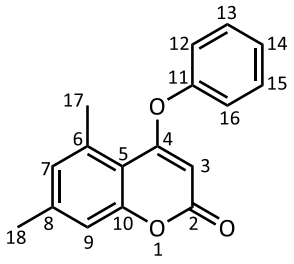
4-Bromo-5,7-dimethyl-2*H*-chromen-2-one (163)[48]



Compound **163** was prepared *via* the procedure described for compound **6** using 4-hydroxy-5,7-dimethyl-2*H*-chromen-2-one **160** (1.0 g, 5.26 mmol, 1.0 equiv.). The residue was recrystallised from EtOH to yield **163** as an orange solid (0.4373 g, 33%); m.p. 160–163 °C (lit.[48] 125–127 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (s, 1H, C(9)**H**), 6.94 (s, 1H, C(7)**H**), 6.80 (s, 1H, C(3)**H**), 2.86 (s, 3H, C(12)**H**$_3$), 2.39 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6 (q**C**-2), 154.1 (q**C**-10), 143.4 (q**C**-8), 139.7 (q**C**-6), 137.4 (q**C**-4), 130.4 (**C**(7)H), 120.4 (**C**(3)H), 116.3 (**C**(9)H), 114.8 (q**C**-5), 24.4 (**C**(12)H_3), 21.3 (**C**(11)H_3); *m/z* (ES+): 252 (^{79}Br (M+H)$^+$ 42%), 254 (^{81}Br (M+H)$^+$ 38%).

Spectral characteristics were consistent with previously reported data.[48]

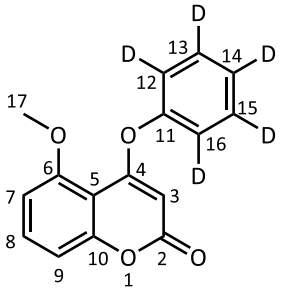
5,7-Dimethyl-4-phenoxy-2*H*-chromen-2-one (164)



Compound **164** was prepared *via* the procedure described for compound **97** using 4-bromo-5,7-dimethyl-2*H*-chromen-2-one **163** (200 mg, 0.79 mmol, 1.0 equiv.) and phenol (82 mg, 0.87 mmol, 1.1 equiv.). The residue was purified by column chromatography (EtOAc:hexanes 10:90) to yield **164** as a white solid (0.036 g, 17%); m.p. 130–133 °C; IR ν_{max} (film) 1718 (ester C=O stretch), 1611 (aromatic C–C stretch), 1369 (ester C–O stretch), 1194 (ether C–O stretch); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (t, *J* = 7.8, 2H, C(13)**H** & C(15)**H**), 7.33 (t, *J* =

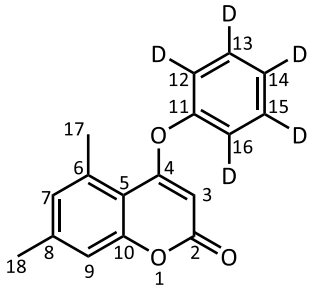
7.4, 1H, C(14)**H**), 7.15 (d, *J* = 7.8, 2H, C(12)**H** & C(16)**H**), 7.03 (s, 1H, C(9)**H**), 6.94 (s, 1H, C(7)**H**), 5.33 (s, 1H, C(3)**H**), 2.76 (s, 3H, C(17)$\mathbf{H}_3$), 2.41 (s, 3H, C(18)$\mathbf{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4 (q**C**-4), 162.8 (q**C**-2), 155.3 (q**C**-10), 152.2 (q**C**-11), 143.1 (q**C**-8), 136.7 (q**C**-6), 130.5 (**C**(13)H & **C**(15)H), 129.0 (**C**(7)H), 126.7 (**C**(14)H), 121.4 (**C**(12)H & **C**(16)H), 115.5 (**C**(9)H), 111.7 (q**C**-5), 93.0 (**C**(3)H), 23.3 (**C**(17)H_3), 21.5 (**C**(18)H_3); *m/z* (ES+): 267 ((M+H)$^+$ 8%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{17}H_{15}O_3$ 267.1021; Found 267.1034.

5-Methoxy-4-(phenoxy-*d*$_5$)-2*H*-chromen-2-one (165)



Compound **165** was prepared *via* the procedure described for compound **97** using 4-bromo-5-methoxy-2*H*-chromen-2-one **161** (390 mg, 1.529 mmol, 1.0 equiv.) and phenol-d_6 (168 mg, 1.682 mmol, 1.1 equiv.). The residues were purified by column chromatography (EtOAc:hexanes 20:80) to yield **165** as a white solid (0.116 g, 28%); m.p. 212–217 °C; IR ν_{max} (film) 1704 (ester C=O stretch), 1612 (alkene C=C stretch), 1471 (aromatic C–C stretch), 1255 (ester C–O stretch), 1189 (ether C–O stretch), 1094 (ether C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (t, *J* = 8.4, 1H, C(8)**H**), 6.97 (dd, *J* = 8.4, 0.9, 1H, C(7)**H**), 6.80 (d, *J* = 8.4, 1H, C(9)**H**), 5.33 (s, 1H, C(3)**H**), 3.92 (s, 3H, C(17)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6 (q**C**-4), 162.4 (q**C**-2), 158.0 (q**C**-6), 155.7 (q**C**-11), 152.8 (q**C**-10), 132.8 (**C**(7)H), 129.8 (t, *J* = 25, q**C**-13 & q**C**-15), 125.9 (t, *J* = 24, q**C**-14), 120.9 (t, *J* = 25, q**C**-12 & q**C**-16), 109.7 (**C**(9)H), 106.8 (**C**(8)H), 105.8 (q**C**-5), 93.5 (**C**(3)H), 56.5 (**C**(17)H_3); *m/z* (ES+): 274 ((M+H)$^+$ 70%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{16}H_8D_5O_4$ 274.1128; Found 274.1118.

5,7-Dimethyl-4-(phenoxy-d$_5$)-2*H*-chromen-2-one (166)



Compound **166** was prepared *via* the procedure described for compound **97** using 4-bromo-5,7-dimethyl-2*H*-chromen-2-one **163** (190 mg, 0.75 mmol, 1.0 equiv.) and phenol-d_6 (83 mg, 0.83 mmol, 1.1 equiv.). The residue was purified by column chromatography (EtOAc:hexanes 10:90) to yield **166** as a white solid (0.036 g, 17%); m.p.

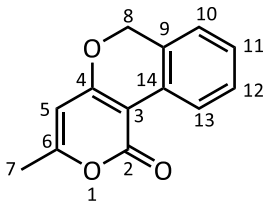
129–132 °C; IR ν_{max} (film) 1715 (ester C=O stretch), 1613 (aromatic C–C stretch), 1366 (ester C–O stretch), 1232 (ether C–O stretch); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H, C(9)**H**), 6.94 (s, 1H, C(7)**H**), 5.33 (s, 1H, C(3)**H**), 2.76 (s, 3H, C(17)$\mathbf{H}_3$), 2.41 (s, 3H, C(18)$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4 (q**C**-4), 162.8 (q**C**-2), 155.3 (q**C**-10), 152.2 (q**C**-11), 143.0 (q**C**-8), 136.7 (q**C**-6), 130.0 (t, *J* = 25, q**C**-13 & q**C**-15), 129.0 (**C**(7)H), 126.2 (t, *J* = 24, q**C**-14), 121.0 (t, *J* = 25, q**C**-12 & q**C**-16), 115.5 (**C**(9)H), 111.7 (q**C**-5), 93.0 (**C**(3)H), 23.3 (**C**(17)H_3), 21.5 (**C**(18)H_3); *m/z* (ES+): 272 ($(M+H)^+$ 10%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{10}D_5O_3$ 272.1335; Found 272.1336.

5.3. Palladium-catalysed intramolecular direct arylation

5.3.1. Palladium/pivalic acid-mediated direct arylation

General Procedure: A Schlenk tube was heated under vacuum and refilled with N_2 three times. Dry Na_2CO_3 (3.0 equiv.) was added to a Schlenk tube. The Schlenk was heated under vacuum and refilled with N_2 twice. $Pd_2(dba)_3$ (2 mol%), PPh_3 (4 mol%), PivOH (30 mol%) and substrate (1.0 equiv.) were added. The Schlenk was evacuated and refilled with N_2 twice. Anhydrous NMP (3 mL) was added and the Schlenk tube was placed in an oil bath preheated to 130 °C. After 2-6 h, the mixture was allowed to cool to ambient temperature and diluted with water (10 mL) and EtOAc (10 mL). The organic layers were extracted with EtOAc (2 × 10 mL) and washed with 1 M aqueous HCl (1 × 20 mL), H_2O (3 × 10 mL) and brine (1 × 20 mL). The combined organic extracts were dried, filtered and concentrated under reduced pressure. The residue was purified by column chromatography.

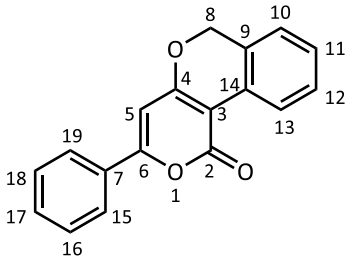
3-Methylpyrano[4,3-*c*]isochromen-1(6*H*)-one (31)[10]



4-((2-Iodobenzyl)oxy)-6-methyl-2*H*-pyran-2-one **4** (100 mg, 0.292 mmol, 1.0 equiv.) was used as the substrate in the General Procedure, except that $Pd_2(dba)_3$ (5 mol%) and PPh_3 (10 mol%) were used, and stirred at 130 °C for 2 h. The residue was purified by column chromatography (EtOAc:hexanes 25:75) to afford **31** as a yellow solid (0.048 g, 77%); m.p. 141–144 °C (lit. [10] 110-113 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, *J* = 7.9, 1H, C(13)**H**), 7.30 – 7.44 (m, 1H, C(11)**H**), 7.30 – 7.19 (m, 1H C(10)**H**), 7.08 – 6.98 (m, 1H, C(12)**H**), 5.90 (s, 1H, C(5)**H**), 5.23 (s, 2H, C(8)$\mathbf{H}_2$), 2.26 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2 (q**C**-4), 162.5 (q**C**-2), 161.6 (q**C**-6), 128.9 (**C**(11)H), 127.5 (**C**(12)H), 126.8 (q**C**-9), 126.5 (q**C**-14), 124.0 (**C**(13)H), 123.7 (**C**(10)H), 100.2 (**C**(5)H), 99.8 (q**C**-3), 69.3 (**C**(8)H_2), 20.1 (**C**(7)H_3); *m/z* (ES+): 215 ($(M+H)^+$ 44%).

Spectal data were consistent with previously reported data.[10]

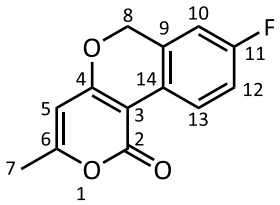
3-Phenylpyrano[4,3-*c*]isochromen-1(6*H*)-one (33)[2]



4-((2-Bromobenzyl)oxy)-6-phenyl-2*H*-pyran-2-one **9** (45 mg, 0.126 mmol, 1.0 equiv.) was used as the substrate in the General Procedure and stirred at 130 °C for 3 h. The residue was purified by column chromatography (DCM) to afford a yellow solid **33** (0.0214 g, 61%); m.p. 124–130 °C (lit.[2] 137 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (dd, *J* = 7.9, 0.8, 1H, C(13)**H**), 7.92 – 7.82 (m, 2H, 2 × ArC**H**), 7.49 – 7.44 (m, 3H, 3 × ArC**H**), 7.44 – 7.36 (m, 1H, ArC**H**), 7.28 (td, *J* = 7.5, 1.3, 1H, C(12)**H**), 7.08 (dd, *J* = 7.5, 0.8, 1H, C(10)**H**), 6.57 (s, 1H, C(5)**H**), 5.30 (s, 2H, C(8)$\mathbf{H}_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1 (q**C**-4), 160.9 (q**C**-6), 160.1 (q**C**-2), 131.1 (Ar**C**H), 130.0 (q**C**-14), 129.0 (3 × Ar**C**H), 127.8 (Ar**C**H), 127.1 (q**C**-7), 126.5 (q**C**-9), 125.7 (2 × Ar**C**H), 124.3 (Ar**C**H), 123.8 (Ar**C**H), 101.1 (q**C**-3), 97.6 (**C**(5)H), 69.4 (**C**(8)H_2); *m/z* (ES+): 277 ($(M+H)^+$ 100%).

Spectal data were consistent with previously reported data.[2]

8-Fluoro-3-methylpyrano[4,3-*c*]isochromen-1(6*H*)-one (34)[7]

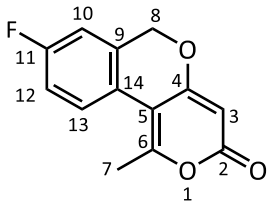


4-((2-Bromo-5-fluorobenzyl)oxy)-6-methyl-2*H*-pyran-2-one **12** (100 mg, 0.319 mmol, 1.0 equiv.) was used as the substrate in the General Procedure and stirred at 130 °C for 3 h. The residue was purified by column chromatography (DCM) to afford **34** as a yellow solid (0.048 g, 65%) and **35** as a yellow solid (0.011 g, 15%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 8.9, 5.6, 1H, C(13)**H**), 7.03 (td, *J* = 8.8, 2.6, 1H, C(12)**H**), 6.76 (dd, *J* = 8.4, 2.6, 1H, C(10)**H**), 5.91 (s, 1H, C(5)**H**), 5.20 (s, 2H, C(8)$\mathbf{H}_2$), 2.26 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6 (q**C**-4), 163.6 (q**C**-2), 161.6 (d, *J* = 156, q**C**-11), 160.4 (q**C**-6), 129.0 (d, *J* = 7, q**C**-9), 126.2 (d, *J* = 8, **C**(13)H), 122.5 (q**C**-14), 115.5 (d, *J* = 21, **C**(12)H), 111.1 (d, *J* = 23, **C**(10)H), 100.1 (**C**(5)H), 99.4 (q**C**-3), 68.8 (**C**(8)H_2), 20.1 (**C**(7)H_3).

Spectal data were consistent with previously reported data.[7]

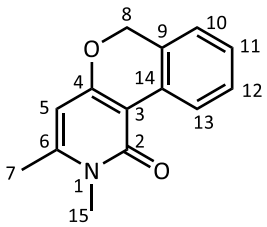
8-Fluoro-1-methylpyrano[4,3-c]isochromen-3(6*H*)-one (35)[7]



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 8.7, 5.0, 1H, C(13)**H**), 7.14 (td, *J* = 8.5, 2.7, 1H, C(12)**H**), 6.97 (dd, *J* = 8.2, 2.5, 1H, C(10)**H**), 5.78 (s, 1H, C(3)**H**), 5.03 (s, 2H, C(8)$\mathbf{H}_2$), 2.62 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4 (q**C**-4), 163.3 (q**C**-2), 161.7 (d, *J* = 250, q**C**-11), 159.2 (q**C**-6), 133.7 (d, *J* = 8, q**C**-9), 127.6 (d, *J* = 8, **C**(13)H), 122.3 (d, *J* = 3, q**C**-14), 115.9 (d, *J* = 22, **C**(12)H), 112.6 (d, *J* = 23, **C**(10)H), 106.9 (q**C**-5), 93.7 (**C**(3)H), 68.9 (d, *J* = 2, **C**(8)H_2), 20.5 (**C**(7)H_3).

Spectal data were consistent with previously reported data.[7]

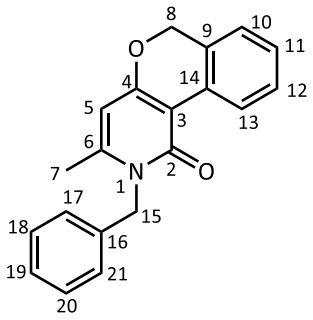
2,3-Dimethyl-2,6-dihydro-1*H*-isochromeno[4,3-*c*]pyridin-1-one (36)[10]



4-((2-Iodobenzyl)oxy)-1,6-dimethylpyridin-2(1*H*)-one **16** (62.5 mg, 0.176 mmol, 1.0 equiv.) was used as the substrate in the General Procedure, except that $Pd_2(dba)_3$ (5 mol%) and PPh_3 (10 mol%) were used, and stirred at 130 °C for 6 h. The residue was purified by column chromatography (DCM) to afford **36** as a pale yellow solid (0.0295 g, 74%); m.p. 89–94 °C (lit.[2] 95–96 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (d, *J* = 8.0, 1H, C(13)**H**), 7.35 (t, *J* = 8.0, 1H, C(11)**H**), 7.21 (t, *J* = 7.4, 1H, C(12)**H**), 7.05 (d, *J* = 7.4, 1H, C(10)**H**), 5.88 (s, 1H, C(5)**H**), 5.10 (s, 2H, C(8)$\mathbf{H}_2$), 3.54 (s, 3H, C(15)$\mathbf{H}_3$), 2.34 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8 (q**C**-4), 160.3 (q**C**-2), 144.4 (q**C**-6), 126.9 (q**C**-14), 126.6 (**C**(11)H), 126.2 (q**C**-9), 124.9 (**C**(12)H), 122.5 (**C**(13)H), 121.8 (**C**(10)H), 103.6 (q**C**-3), 98.3 (**C**(5)H), 67.1 (**C**(8)H_2), 29.1 (**C**(15)H_3), 19.4 (**C**(7)H_3); *m/z* (ES+): 228 ($(M+H)^+$ 100%).

Using 4-((2-bromobenzyl)oxy)-1,6-dimethylpyridin-2(1*H*)-one **15** (100 mg) as the substrate gave **36** (0.019 g, 26%). Spectral characteristics were consistent with previously reported data.[2]

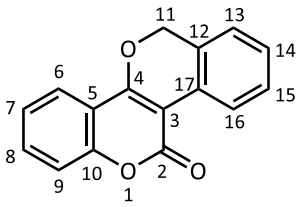
2-Benzyl-3-methyl-2,6-dihydro-1*H*-isochromeno[4,3-*c*]pyridin-1-one (37)[2]



1-Benzyl-4-((2-iodobenzyl)oxy)-6-methylpyridin-2(1*H*)-one **18** (100 mg, 0.232 mmol, 1.0 equiv.) was used as the substrate in the General Procedure, except that $Pd_2(dba)_3$ (5 mol%) and PPh_3 (10 mol%) were used, and stirred at 130 °C for 6 h. The residue was purified by column chromatography (EtOAc:hexanes 20:80) to afford **37** as a pale yellow solid (0.054 g, 77%); m.p. 125–130 °C (lit.[2] 126–127 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (d, *J* = 7.9, 1H, C(13)**H**), 7.39 – 7.14 (m, 7H, C(12)**H**, C(11)**H**, C(17)**H**, C(18)**H**, C(19)**H**, C(20)**H** & C(21)**H**), 7.06 (d, *J* = 7.4, 1H, C(10)**H**), 5.89 (s, 1H, C(5)**H**), 5.38 (s, 2H, C(15)$\mathbf{H}_2$), 5.14 (s, 2H, C(8)$\mathbf{H}_2$), 2.27 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9 (q**C**-4), 162.2 (q**C**-2), 146.5 (q**C**-6), 136.9 (q**C**-16), 128.8 (**C**(18)H & **C**(20)H), 128.7 (q**C**-14), 128.6 (**C**(12)H), 128.0 (q**C**-9), 127.3 (**C**(11)H), 126.9 (**C**(19)H), 126.4 (**C**(17)H & **C**(21)H), 124.5 (**C**(13)H), 123.7 (**C**(10)H), 105.8 (q**C**-3), 100.8 (**C**(5)H), 69.0 (**C**(8)H_2), 47.0 (**C**(15)H_2), 20.9 (**C**(7)H_3); *m/z* (ES+): 304.3 ($(M+H)^+$ 100%).

Using 1-benzyl-4-((2-bromobenzyl)oxy)-6-methylpyridin-2(1*H*)-one **17** (100 mg) as substrate gave **37** (0.033 g, 42%). Spectral characteristics were consistent with previously reported data.[2]

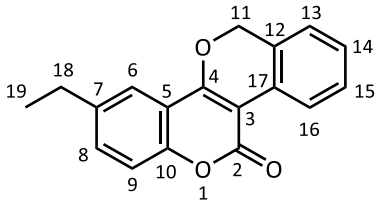
6*H*,11*H*-Isochromeno[4,3-*c*]chromen-11-one (38)[49]



4-((2-Iodobenzyl)oxy)-*2H*-chromen-2-one **20** (50 mg, 0.130 mmol, 1.0 equiv.) was used as the substrate in the General Procedure and stirred at 130 °C for 3 h. The residue was purified by column chromatography (DCM) to afford **38** as a red-brown solid (0.020 g, 61%); m.p. 131–134 °C (lit.[49] 154 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, *J* = 7.8, 1H, C(16)**H**), 7.86 (dd, *J* = 8.0, 1.5, 1H, C(6)**H**), 7.59 – 7.52 (1H, m, C(8)**H**), 7.45 – 7.26 (m, 4H, C(7)**H**, C(13)**H**, C(14)**H**, C(15)**H**), 7.12 (d, *J* = 7.5, 1H, C(9)**H**), 5.40 (s, 2H, C(11)$\mathbf{H}_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2 (q**C**-4), 160.1 (q**C**-2), 152.9 (q**C**-10), 132.5 (**C**(8)H), 129.0 (**C**(14)H), 128.2 (**C**(15)H), 127.4 (q**C**-17), 126.7 (q**C**-12), 124.9 (**C**(16)H), 124.0 (**C**(7)H), 123.9 (**C**(13)H), 123.1 (**C**(6)H), 116.5 (**C**(9)H), 115.2 (q**C**-5), 102.7 (q**C**-3), 69.8 (**C**$(11)_2$); *m/z* (ES+): 251 ($(M+H)^+$ 88%).

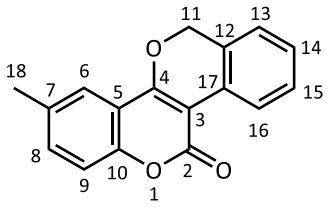
Spectral characteristics were consistent with previously reported data.[49]

3-Ethyl-6*H*,11*H*-isochromeno[4,3-*c*]chromen-11-one (39)



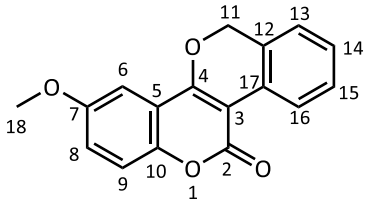
6-Ethyl-4-((2-iodobenzyl)oxy)-*2H*-chromen-2-one **26** (100 mg, 0.246 mmol, 1.0 equiv.) was used as the substrate in the General Procedure and stirred at 130 °C for 3 h. The residue was purified by column chromatography (DCM) to afford **39** as an orange solid (0.049 g, 71%); m.p. 72–75 °C; IR ν_{max} (KBr) 1710 (ester C=O stretch), 1621 (alkene C=C stretch), 1566 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 7.9, 0.7, 1H, C(16)**H**), 7.64 (d, *J* = 1.9, 1H, C(6)**H**), 7.44 – 7.18 (m, 4H, C(8)**H**, C(13)**H**, C(14)**H**, C(15)**H**), 7.14 – 7.06 (m, 1H, C(9)**H**), 5.36 (s, 2H, C(11)$\mathbf{H}_2$), 2.70 (q, *J* = 7.6, 2H, C(18)$\mathbf{H}_2$), 1.27 (t, *J* = 7.6, 3H, C(19)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3 (q**C**-4), 160.3 (q**C**-2), 151.2 (q**C**-10), 140.2 (q**C**-7), 132.5 (**C**(8)H), 129.0 (**C**(14)H), 128.1 (**C**(15)H), 127.4 (q**C**-17), 126.8 (q**C**-12), 124.9 (**C**(16)H), 123.9 (**C**(13)H), 121.5 (**C**(6)H), 116.3 (**C**(9)H), 114.9 (q**C**-5), 102.4 (q**C**-3), 69.7 (**C**$(11)H_2$), 28.4 (**C**$(18)H_2$), 15.6 (**C**$(19)H_3$); *m/z* (ES+): 279 ($(M+H)^+$ 2%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{15}O_3$ 279.1021; Found 279.1019.

3-Methyl-6*H*,11*H*-isochromeno[4,3-*c*]chromen-11-one (40)[50]



6-Methyl-4-((2-iodobenzyl)oxy)-*2H*-chromen-2-one **27** (40 mg, 0.102 mmol, 1.0 equiv.) was used as the substrate in the General Procedure and stirred at 130 °C for 3 h. The residue was purified by column chromatography (DCM) to afford **40** as an off-white solid (0.226 g, 71%); m.p. 155–159 °C (lit.[50] 165 °C); 1H NMR (300 MHz, $CDCl_3$) δ 8.55 (dd, *J* = 7.9, 0.8, 1H, C(16)**H**), 7.66 – 7.61 (m, 1H, C(6)**H**), 7.46 – 7.16 (m, 4H, 4 × ArC**H**), 7.15 – 7.06 (m, 1H, C(9)**H**), 5.37 (s, 2H, C(11)$\mathbf{H}_2$), 2.41 (s, 3H, C(18)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2 (q**C**-4), 160.3 (q**C**-2), 151.1 (q**C**-10), 133.8 (q**C**-7), 133.6 (**C**(8)H), 129.0 (**C**(14)H), 128.1 (**C**(15)H), 127.4 (q**C**-17), 126.8 (q**C**-12), 124.9 (**C**(16)H), 123.9 (**C**(13)H), 122.7 (**C**(6)H), 116.3 (**C**(9)H), 114.8 (q**C**-5), 102.5 (q**C**-3), 69.7 (**C**(11)H_2), 20.9 (**C**(18)H_3); *m/z* (ES+): 265 ($(M+H)^+$ 28%).

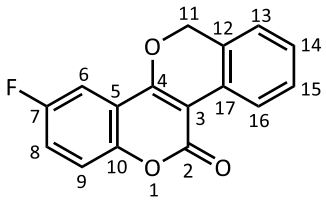
3-Methoxy-6*H*,11*H*-isochromeno[4,3-*c*]chromen-11-one (41)[7]



4-((2-Iodobenzyl)oxy)-6-methoxy-*2H*-chromen-2-one **28** (20 mg, 0.049 mmol, 1.0 equiv.) was used as the substrate in the General Procedure and stirred at 130 °C for 3 h. The residue was purified by column chromatography (DCM) to afford **41** as a white solid (0.0113 g, 82%); m.p. 138–139 °C (lit.[7] 178–179 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 8.0, 0.7, 1H, C(16)**H**), 7.41 (td, *J* = 7.8, 1.3, 1H, C(15)**H**), 7.36 – 7.23 (m, 3H, C(9)**H**, C(13)**H** & C(14)**H**), 7.19 – 7.09 (m, 2H, C(6)**H** & C(8)**H**), 5.40 (s, 2H, C(11)**H**), 3.87 (s, 3H, C(18)**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9 (q**C**-4), 160.3 (q**C**-2), 156.0 (q**C**-7), 147.5 (q**C**-10), 129.1 (**C**(16)H), 128.3 (**C**(14)H), 127.4 (q**C**-17), 126.8 (q**C**-12), 125.0 (**C**(15)H), 123.9 (**C**(9)H), 121.0 (**C**(13)H), 117.7 (**C**(8)H), 115.5 (q**C**-5), 104.5 (**C**(6)H), 102.8 (q**C**-3), 69.8 (**C**(11)H_2), 55.9 (**C**(18)H_3); *m/z* (ES+): 281 ($(M+H)^+$ 100%).

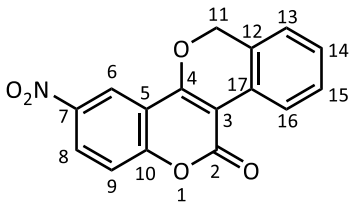
Spectral characteristics were consistent with previously reported data.[7]

3-Fluoro-6*H*,11*H*-isochromeno[4,3-*c*]chromen-11-one (42)



6-Fluoro-4-((2-iodobenzyl)oxy)-2*H*-chromen-2-one **29** (100 mg, 0.252 mmol, 1.0 equiv.) was used as the substrate in the General Procedure and stirred at 130 °C for 3 h. The residue was purified by column chromatography (DCM) to afford **42** as a yellow solid (0.029 g, 43%); m.p. 154–157 °C; IR ν_{max} (film) 1710 (C=O stretch), 1563 (C=C stretch), 1178 (C-O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 7.9, 0.9, 1H, C(16)**H**), 7.51 (ddd, *J* = 8.3, 2.8, 0.6, 1H, C(13)**H**), 7.41 (td, *J* = 7.7, 1.5, 1H, C(15)**H**), 7.37 – 7.21 (m, 3H, C(6)**H**, C(9)**H** & C(14)**H**), 7.17 – 7.09 (m, 1H, C(8)**H**), 5.41 (s, 2H, C(11)$\mathbf{H}_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2 (d, *J* = 3, q**C**-4), 159.8 (q**C**-2), 158.7 (d, *J* = 244, q**C**-7), 149.0 (d, *J* = 2, q**C**-10), 129.1 (**C**(14)H), 128.6 (**C**(15)H), 127.4 (q**C**-17), 126.2 (q**C**-12), 125.0 (**C**(16)H), 124.0 (**C**(13)H), 120.1 (d, *J* = 25, **C**(8)H), 118.2 (d, *J* = 8, **C**(9)H), 116.1 (d, *J* = 9, q**C**-5), 108.7 (d, *J* = 26, **C**(6)H), 103.3 (q**C**-3), 69.9 (**C**(11)H_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ -117 (s, C(7)**F**); *m/z* (ES+): 277 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{10}O_3F$ 269.0614; Found 269.0617; Anal. Calcd for $C_{16}H_9FO_3$: C, 71.64; H, 3.38. Found: C, 71.49; H, 3.58.

3-Nitro-6*H*,11*H*-isochromeno[4,3-*c*]chromen-11-one (43)



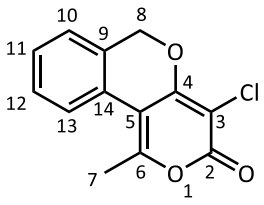
4-((2-Iodobenzyl)oxy)-6-nitro-*2H*-chromen-2-one **30** (40 mg, 0.095 mmol, 1.0 equiv.) was used as the substrate in the General Procedure and stirred at 130 °C for 3 h. The residue was purified by column chromatography (DCM) to afford **43** as a yellow solid (0.0161 g, 58%); m.p. 222–225 °C; IR ν_{max} (film) 1722 (C=O stretch), 1613 (C=C stretch), 1531 (N–O asymmetric stretch), 1347 (N–O symmetric stretch), 1334 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (d, *J* = 2.6, 1H, C(6)**H**), 8.52 (dd, *J* = 7.6, 1.4, 1H, C(16)**H**), 8.41 (dd, *J* = 9.1, 2.7, 1H, C(8)**H**), 7.50 – 7.33 (m, 3H, C(9)**H**, C(14)**H** & C(15)**H**), 7.20 – 7.13 (m, 1H, C(13)**H**), 5.50 (s, 2H, C(11)$\mathbf{H}_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5 (q**C**-4), 158.6 (q**C**-2), 156.0 (q**C**-10), 144.0 (q**C**-7), 129.3 (**C**(9)H), 129.2 (**C**(15)H), 127.3 (q**C**-17), 127.0 (**C**(8)H), 125.5 (q**C**-12), 125.1 (**C**(16)H), 124.2 (**C**(13)H), 119.7 (**C**(6)H), 117.7 (**C**(14)H),

115.7 (q**C**-5), 104.0 (q**C**-3), 70.1 (**C**(11)H_2); Anal. Calcd for $C_{16}H_9O_5N$: C, 65.09; H, 3.07; N, 4.74. Found: C, 64.35; H, 2.72; N, 4.76.

5.3.2. Palladium-mediated C–5 direct arylation

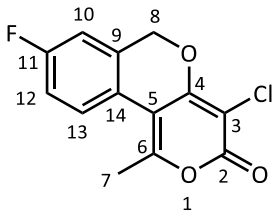
General Procedure: A Schlenk tube was heated under vacuum and refilled with N_2 three times. KOAc (2.5 equiv.) was added. The Schlenk tube was heated under vacuum and refilled with N_2 twice. Allowed Schlenk tube to cool to ambient temperature. Substrate (1.0 equiv.), $Pd(OAc)_2$ (5 mol%) and TBAB (1.2 equiv.) were added. The Schlenk tube was evacuated and refilled with N_2 three times. Freshly distilled THF (4 mL) was added *via* syringe. The Schlenk tube was placed in an oil bath preheated to 76 °C. The reaction mixture was stirred at this temperature for 18 h, then cooled to ambient temperature. The mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (DCM).

4-Chloro-1-methyl-3*H*,6*H*-pyrano[4,3-*c*]isochromen-3-one (64)



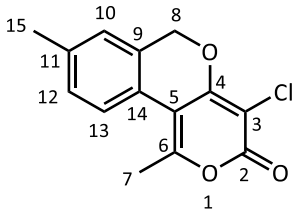
3-Chloro-4-((2-iodobenzyl)oxy)-6-methyl-2*H*-pyran-2-one **47** (50.0 mg, 0.133 mmol, 1.0 equiv.) was used as the substrate in the General Procedure, except that $Pd(OAc)_2$ (2 mol%) and TBAB (1.0 equiv.) were used, to yield **64** as a white solid (0.028 g, 85%); m.p. 155–158 °C; IR ν_{max} (film) 1726 (ester C=O stretch), 1638 (alkene C=C stretch), 1544 (aromatic C–C stretch), 1185 (C–O stretch), 770 (C–Cl stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.42 (m, 2H, C(12)**H** & C(13)**H**), 7.38 (td, *J* = 7.3, 1.7, 1H, C(11)**H**), 7.27 (d, *J* = 7.4, 1H, C(10)**H**), 5.19 (s, 2H, C(8)$\mathbf{H}_2$), 2.65 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1 (q**C**-4), 159.9 (q**C**-2), 156.9 (q**C**-6), 131.0 (q**C**-14), 129.1 (**C**(13)H), 128.2 (**C**(12)H), 125.7 (**C**(11)H), 125.6 (q**C**-9), 125.4 (**C**(10)H), 107.8 (q**C**-5), 100.8 (q**C**-3), 70.2 (**C**(8)H_2), 20.3 (**C**(7)H_3); *m/z* (ES+): 249 (^{35}Cl (M+H)$^+$ 16%), 251 (^{37}Cl (M+H)$^+$ 6%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{13}H_{10}ClO_3$ 249.0318; Found 249.0318.

4-Chloro-8-fluoro-1-methyl-3*H*,6*H*-pyrano[4,3-*c*]isochromen-3-one (66)



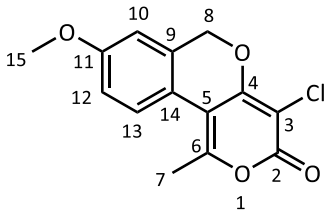
2-Pyrone **50** (28.0 mg, 0.071 mmol, 1.0 equiv.) was used as the substrate in the General Procedure to yield **66** as an off-white solid (0.012 g, 43%); m.p. 147–151 °C; IR ν_{max} (film) 1733 (ester C=O stretch), 1635 (alkene C=C stretch), 1549 (aromatic C–C stretch), 1185 (ester C–O stretch), 1027 (ether C–O stretch), 834 (C–Cl stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 8.8, 5.0, 1H, C(13)**H**), 7.17 (td, *J* = 8.6, 2.7, 1H, C(12)**H**), 7.01 (dd, *J* = 8.0, 2.6, 1H, C(10)**H**), 5.17 (s, 2H, C(8)$\mathbf{H}_2$), 2.63 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6 (q**C**-4), 162.0 (d, *J* = 251, q**C**-11), 159.7 (q**C**-2), 156.5 (d, *J* = 2, q**C**-6), 133.3 (d, *J* = 8, q**C**-9), 127.8 (d, *J* = 8, **C**(13)H), 121.8 (d, *J* = 3, q**C**-14), 116.2 (d, *J* = 22, **C**(12)H), 112.7 (d, *J* = 23, **C**(10)H), 107.2 (q**C**-5), 101.2 (q**C**-3), 69.6 (d, *J* = 2, **C**(8)H_2), 20.2 (**C**(7)H_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -112 (s, C(11)**F**); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_9ClFO_3$ 267.0224; Found 267.0229.

4-Chloro-1,8-dimethyl-3*H*,6*H*-pyrano[4,3-*c*]isochromen-3-one (67)



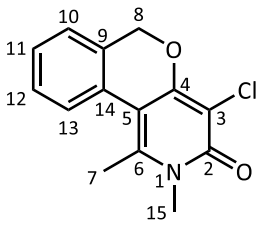
2-Pyrone **48** (30.0 mg, 0.077 mmol, 1.0 equiv.) was used as the substrate in the General Procedure to yield **67** as a pale orange solid (0.016 g, 53%); m.p. 158–163 °C; IR ν_{max} (film) 1726 (ester C=O stretch), 1636 (alkene C=C stretch), 1548 (aromatic C–C stretch), 1301 (ester C–O stretch), 1190 (ether C–O stretch), 825 (C–Cl stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.1, 1H, C(13)**H**), 7.25 (d, *J* = 8.4, 1H, C(12)**H**), 7.08 (s, 1H, C(10)**H**), 5.16 (s, 2H, C(8)$\mathbf{H}_2$), 2.63 (s, 3H, C(7)$\mathbf{H}_3$), 2.40 (s, 3H, C(15)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1 (q**C**-4), 160.0 (q**C**-2), 156.2 (q**C**-6), 138.4 (q**C**-14), 130.9 (q**C**-11), 129.8 (Ar**C**H), 126.0 (Ar**C**H), 125.6 (Ar**C**H), 122.7 (q**C**-9), 107.8 (q**C**-5), 100.8 (q**C**-3), 70.2 (**C**(8)H_2), 21.2 (**C**(15)H_3), 20.2 (**C**(7)H_3); *m/z* (ES+): 263 (^{35}Cl $(M+H)^+$ 18%), 265 (^{37}Cl $(M+H)^+$ 6%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{12}ClO_3$ 263.0475; Found 263.0471.

4-Chloro-8-methoxy-1-methyl-3*H*,6*H*-pyrano[4,3-*c*]isochromen-3-one (68)



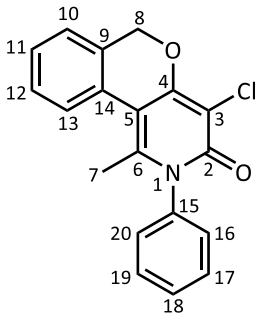
2-Pyrone **52** (30.0 mg, 0.074 mmol, 1.0 equiv.) was used as the substrate in the General Procedure. The resulting crude product was purified by column chromatography (MeOH:DCM 0.5:99.5) to give **68** as a pale orange solid (0.013 g, 63%); m.p. 193–197 °C; IR ν_{max} (film) 1728 (ester C=O stretch), 1635 (alkene C=C stretch), 1544 (aromatic C–C stretch), 1140 (ester C–O stretch), 1052 (ether C–O stretch), 934 (C–Cl stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.7, 1H, C(13)**H**), 6.98 (dd, *J* = 8.7, 2.7, 1H, C(12)**H**), 6.79 (d, *J* = 2.6, 1H, C(10)**H**), 5.16 (s, 2H, C(8)$\mathbf{H}_2$), 3.86 (s, 3H, C(15)$\mathbf{H}_3$), 2.61 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9 (q**C**-4), 160.0 (q**C**-2), 159.4 (q**C**-11), 155.3 (q**C**-9), 132.6 (q**C**-6), 127.2 (C(13)**H**), 117.8 (q**C**-14), 114.7 (C(10)**H**), 110.7 (C(12)**H**), 107.6 (q**C**-5), 100.9 (q**C**-3), 70.2 (C(8)$\mathbf{H}_2$), 55.5 (C(15)$\mathbf{H}_3$), 20.2 (C(7)$\mathbf{H}_3$); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{12}ClO_4$ 279.0424; Found 279.0428.

4-Chloro-1,2-dimethyl-2,6-dihydro-3*H*-isochromeno[4,3-*c*]pyridin-3-one (70)



2-Pyridone **62** (30.0 mg, 0.077 mmol, 1.0 equiv.) was used as the substrate in the General Procedure, except that the mixture was stirred for 24 h. The residue was purified by column chromatography (DCM:MeOH 99.7:0.3) to yield **70** as a white solid (0.011 g, 55%); m.p. 218–220 °C; IR ν_{max} (film) 1730 (amide C=O stretch), 1651 (alkene C=C stretch), 1533 (aromatic C–C stretch), 1266 (ether C–O stretch), 738 (C–Cl stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.14 (m, 4H, 4 × ArC**H**), 5.06 (s, 2H, C(8)$\mathbf{H}_2$), 3.70 (s, 3H, C(15)$\mathbf{H}_3$), 2.73 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2 (q**C**-4), 159.6 (q**C**-2), 141.9 (q**C**-Ar), 132.1 (q**C**-Ar), 128.5 (Ar**C**H), 128.5 (q**C**-Ar), 127.0 (Ar**C**H), 126.3 (Ar**C**H), 125.4 (Ar**C**H), 107.9 (q**C**-5), 106.1 (q**C**-3), 70.0 (**C**(8)H_2), 32.6 (**C**(15)H_3), 19.8 (**C**(7)H_3); *m/z* (ES+): 262 (^{35}Cl $(M+H)^+$ 100%), 264 (^{37}Cl $(M+H)^+$ 38%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{13}NO_2Cl$ 262.0635; Found 262.0639.

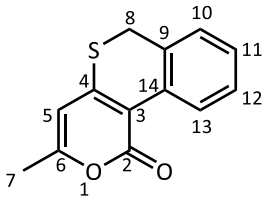
4-Chloro-1-methyl-2-phenyl-2,6-dihydro-3*H*-isochromeno[4,3-*c*]pyridin-3-one (71)



2-Pyridone **63** (30.0 mg, 0.066 mmol, 1.0 equiv.) was used as the substrate in the General Procedure. The residue was purified by column chromatography (EtOAc:hexanes 70:30) to give **71** as a brown solid (0.018 g, 60%); m.p. >250 °C; IR ν_{max} (film) 1655 (amide C=O stretch), 1528 (alkene C=C stretch), 1349 (aromatic C–C stretch), 1206 (ester C–O stretch), 1041 (ether C–O stretch), 700 (C–Cl stretch); ^{1}H NMR (300 MHz, DMSO) δ 7.65 – 7.50 (m, 4H, 4 × ArC**H**), 7.48 – 7.31 (m, 5H, 5 × ArC**H**), 5.23 (s, 2H, C(8)**H**$_2$), 2.27 (s, 3H, C(7)**H**$_3$); ^{13}C NMR (75 MHz, DMSO) δ 160.7 (q**C**-4), 159.6 (q**C**-2), 143.6 (q**C**-15), 139.3 (q**C**-14), 132.5 (q**C**-6), 130.1 (2 × ArC**H**), 129.3 (ArC**H**), 128.9 (ArC**H**), 128.9 (2 × ArC**H**), 128.3 (q**C**-9), 127.4 (ArC**H**), 126.8 (ArC**H**), 125.9 (ArC**H**), 107.1 (q**C**-5), 104.9 (q**C**-3), 69.9 (**C**(8)H$_2$), 21.4 (**C**(7)H$_3$); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{15}NO_2Cl$ 324.0791; Found 324.0787.

5.3.3. Palladium/TBAB-mediated C–3 direct arylation

3-Methyl-1*H*,6*H*-isothiochromeno[4,3-*c*]pyran-1-one (83)

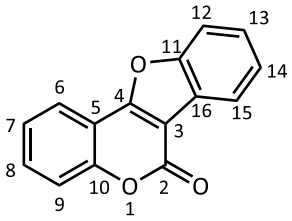


A Schlenk tube was heated under vacuum and refilled with N_2 three times. Dry KOAc (20.6 mg, 0.209 mmol, 2.5 equiv.) was added to a Schlenk tube. The Schlenk was heated under vacuum and refilled with N_2 twice. $Pd(OAc)_2$ (0.4 mg, 0.002 mmol, 2 mol%), TBAB (27.0 mg, 0.084 mmol, 1.0 equiv.) and 4-((2-iodobenzyl)thio)-6-methyl-2*H*-pyran-2-one **82** (30 mg, 0.084 mmol, 1.0 equiv.) were added. The Schlenk was evacuated and refilled with N_2 twice. Toluene (2 mL, previously dried over 4Å molecular sieves) was added and the Schlenk was placed in an oil bath preheated to 127 °C. After 16 h, the mixture was allowed to cool to ambient temperature and diluted with water (10 mL) and EtOAc (10 mL). The organic components were extracted with EtOAc (2 × 10 mL) and washed with 1 M aqueous HCl (1 × 20 mL), H_2O (3 × 10 mL) and brine (1 × 20 mL). The combined organic extracts were dried, filtered and concentrated under reduced pressure. The crude residue (mixture of starting material and product) was purified by column chromatography (DCM) to afford **83** as a yellow solid (0.0040 g, 21%); m.p. 158–162 °C; IR ν_{max} (film) 1705 (ester C=O stretch), 1635 (alkene C=C stretch), 1436 (aromatic C–C stretch), 1325 (ester C– O stretch), 783 (C–I stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 7.8, 1.3, 1H, C(13)**H**), 7.35 (td, *J* = 7.5, 1.6, 1H, C(12)**H**), 7.29 (td, *J* = 7.3, 1.5, 1H, C(10)**H**), 7.19 – 7.13 (m, 1H, C(11)**H**), 6.08 (d, *J* = 0.9, 1H, C(5)**H**), 3.85 (s, 2H, C(8)**H**$_2$), 2.26 (d, *J* = 0.8, 3H, C(7)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6 (q**C**-4), 158.7 (q**C**-2), 153.9 (q**C**-6), 130.4 (q**C**-9), 129.4 (q**C**-14), 128.5 (**C**(13)H), 128.0 (**C**(10)H), 126.7 (**C**(12)H), 126.5 (**C**(11)H), 115.2 (q**C**-3), 105.3 (**C**(5)H), 31.3 (**C**(8)H_2), 19.6 (**C**(7)H_3); *m/z* (ES+): 231 ($(M+H)^+$ 100%). HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{11}O_2S$ 231.0480; Found 231.0476.

5.3.4. Palladium-mediated double C–H activation

General Procedure: To a reaction vial were added substrate (1.0 equiv.), $Pd(OAc)_2$ (10 mol%), NaO*t*Bu (20 mol%), Ag_2O (1.5 equiv.) and PivOH (0.5 M). The vial was capped and placed in a mantle preheated to 140 °C. The mixture was stirred at this temperature until the substrate was fully consumed, then cooled to ambient temperature. The mixture was diluted with DCM and filtered through a plug of celite. The organic layer was washed with 10% (w/v) aqueous NaOH, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (DCM).

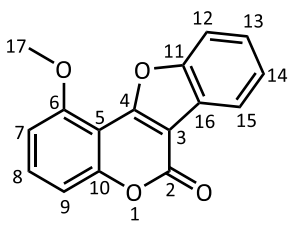
6*H*-Benzofuro[3,2-*c*]chromen-6-one (154)[31]



4-Phenoxy-2*H*-chromen-2-one **97** (60.0 mg, 0.252 mmol, 1.0 equiv.) was used as a substrate in the General Procedure (stirred at 140 °C for 40 min) to yield **154** as a white solid (0.0253 g, 43%); m.p. 180–182 °C (lit.[31] 177–180 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 – 8.05 (m, 1H, C(15)**H**), 7.99 (dd, *J* = 7.8, 1.5, 1H, C(6)**H**), 7.72 – 7.57 (m, 2H, C(8)**H** & C(12)**H**), 7.51 – 7.33 (m, 4H, C(7)**H**, C(9)**H**, C(13)**H** & C(14)**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9 (q**C**-4), 158.0 (q**C**-2), 155.5 (q**C**-11), 153.7 (q**C**-10), 131.9 (**C**(8)H), 126.7 (**C**(13)H), 125.2 (**C**(14)H), 124.6 (**C**(7)H), 123.4 (q**C**-16), 121.8 (**C**(6)H & **C**(15)H), 117.5 (**C**(9)H), 112.6 (q**C**-5), 111.7 (**C**(12)H), 105.8 (q**C**-3); *m/z* (ES+): 237 ($(M+H)^+$ 70%).

Spectral characteristics were consistent with previously reported data.[31]

1-Methoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one (167)



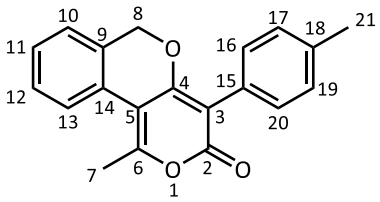
4-Phenoxy-5-methoxy-2*H*-chromen-2-one **162** (13 mg, 0.048 mmol, 1.0 equiv.) was used as a substrate in the General Procedure (stirred at 140 °C for 18 h) to yield **167** as a white solid (0.006 g, 47%); m.p. 205–206 °C; IR ν_{max} (film) 1742 (ester C=O stretch), 1617 (alkene C=C stretch), 1596 (aromatic C–C stretch), 1286 (C–O stretch), 1083 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 – 8.04 (m, 1H, C(15)**H**), 7.80 – 7.66 (m, 1H, C(12)**H**), 7.59 – 7.38 (m, 3H, C(8)**H**, C(13)**H** and C(14)**H**),

7.13 (d, *J* = 8.4 Hz, 1H, C(7)**H**), 6.88 (d, *J* = 8.4, 1H, C(9)**H**), 4.11 (s, 3H, C(17)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8 (q**C**-4), 158.2 (q**C**-2), 156.0 (q**C**-6), 155.6 (q**C**-11), 154.9 (q**C**-10), 132.1 (**C**(8)H), 126.4 (**C**(13)H), 125.1 (**C**(14)H), 123.0 (q**C**-16), 121.5 (**C**(15)H), 111.9 (**C**(12)H), 110.0 (**C**(7)H), 106.1 (**C**(9)H), 105.3 (q**C**-3), 103.8 (q**C**-5), 56.5 (**C**(17)H_3); *m/z* (ES+): 267 ($(M+H)^+$ 10%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{11}O_4$ 267.0657; Found 267.0650.

5.4. Suzuki-Miyaura cross-coupling of 4-chloro-1-methyl-3*H*,6*H*-pyrano[4,3-*c*]isochromen-3-one

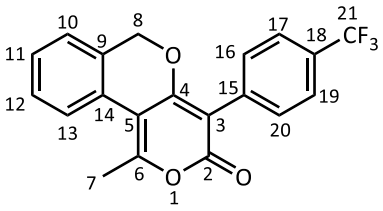
General Procedure: A Schlenk tube was heated under vacuum and refilled with N_2 three times. KOAc (2.2 equiv.) was added. The Schlenk tube was heated under vacuum and refilled with N_2 twice. 3-Chloro-4-((2-iodobenzyl)oxy)-6-methyl-2*H*-pyran-2-one **64** (1.0 equiv.), boronic acid (1.5 equiv.), $Pd(OAc)_2$ (5 mol%) and SPhos (15 mol%) were added. The Schlenk tube was evacuated and refilled with N_2 three times. Freshly distilled THF (0.03 M) was added *via* syringe. The Schlenk tube was placed in an oil bath preheated to 76 °C. The reaction was stirred at this temperature for 18 h, then cooled to ambient temperature. The reaction mixture was diluted with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (DCM).

1-Methyl-4-(*p*-tolyl)-3*H*,6*H*-pyrano[4,3-*c*]isochromen-3-one (87)



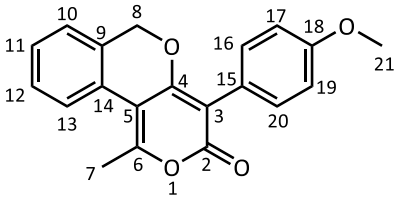
p-Tolylboronic acid (24.6 mg, 0.181 mmol, 1.5 equiv.) was used in the General Procedure to yield **87** as an orange solid (0.0337 g, 92%); m.p. 159–164 °C; IR ν_{max} 1711 (ester C=O stretch), 1555 (aromatic C–C stretch), 1161 (ether C–O stretch), 1013 (alkene C–H bend); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.7, 1H, ArC**H**), 7.49 – 7.29 (m, 4H, 4 × ArC**H**), 7.22 ($_{app}$d, *J* = 8.3, 3H, 3 × ArC**H**), 5.00 (s, 2H, C(8)**H**$_2$), 2.68 (s, 3H, C(21)**H**$_3$), 2.37 (s, 3H, C(7)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5 (q**C**-4), 163.4 (q**C**-2), 157.7 (q**C**-6), 137.6 (q**C**-18), 131.7 (q**C**-14), 130.3 (**C**(16)H & **C**(20)H), 128.8 (**C**(12)H), 128.7 (**C**(17)H & **C**(19)H), 128.0 (q**C**-15), 127.6 (**C**(11)H), 126.8 (q**C**-9), 125.9 (**C**(13)H), 125.2 (**C**(10)H), 107.9 (q**C**-5), 107.1 (q**C**-3), 69.6 (**C**(8)H_2), 21.3 (**C**(21)H_3), 20.3 (**C**(7)H_3); *m/z* (ES+): 305 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{17}O_3$ 305.1178; Found 305.1174.

1-Methyl-4-(4-(trifluoromethyl)phenyl)-3*H*,6*H*-pyrano[4,3-*c*]isochromen-3-one (88)



4-(Trifluoromethyl)phenylboronic acid (46.0 mg, 0.242 mmol, 1.5 equiv.) was used in the General Procedure to yield **88** as a white solid (0.033 g, 57%); m.p. 188–191 °C; IR ν_{max} (film) 1713 (ester C=O stretch), 1110 (ether C–O stretch), 845 (alkene C–H bend); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 4H, C(16)**H**, C(17)**H**, C(19)**H** & C(20)**H**), 7.54 (d, *J* = 7.6, 1H, C(13)**H**), 7.47 (td, *J* = 7.7, 1.2, 1H, C(12)**H**), 7.37 (td, *J* = 7.4, 1.2, 1H, C(11)**H**), 7.25 (d, *J* = 6.9, 1H, C(10)**H**), 5.03 (s, 2H, C(8)$\mathbf{H}_2$), 2.70 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3 (q**C**-4), 162.8 (q**C**-2), 158.7 (q**C**-6), 134.9 (d, *J* = 1, q**C**-15), 131.4 (q**C**-14), 130.9 (**C**(16)H & **C**(20)H), 129.5 (q, *J* = 32, q**C**-18), 129.0 (**C**(12)H), 127.9 (**C**(11)H), 126.4 (q**C**-9), 125.9 (**C**(13)H), 125.3 (**C**(10)H), 124.8 (q, *J* = 4, **C**(17)H & **C**(19)H), 124.2 (q, *J* = 272, q**C**-21), 107.9 (q**C**-5), 105.7 (q**C**-3), 69.8 (**C**(8)H_2), 20.4 (**C**(7)H_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -63 (s, C(21)$\mathbf{F}_3$); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{14}F_3O_3$ 359.0895; Found 359.0885.

4-(4-Methoxyphenyl)-1-methyl-3*H*,6*H*-pyrano[4,3-*c*]isochromen-3-one (89)



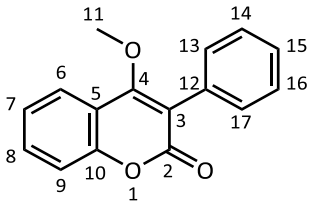
4-(Methoxy)phenylboronic acid (36.8 mg, 0.242 mmol, 1.5 equiv.) was used in the General Procedure. The ^{1}H NMR spectrum of the crude reaction mixture indicated 28% conversion from starting material **64** to product **89**. The residue was purified by column chromatography (MeOH:DCM 1:99) to yield **89** as an impure mixture (contaminated with starting material **64**), yellow solid (0.011 g, approx. 20%). The NMR signals belonging to the title compound could be assigned as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 – 7.10 (m, 7H, 7 × ArC**H**), 6.95 (d, *J* = 8.8 Hz, 1H, ArC**H**), 5.00 (s, 2H, C(8)$\mathbf{H}_2$), 3.83 (s, 3H, C(21)$\mathbf{H}_3$), 2.67 (s, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5 (q**C**-4), 163.3 (q**C**-2), 159.0 (q**C**-18), 157.5 (q**C**-6), 131.7 (q**C**-14), 131.7 (**C**(16)H & **C**(20)H), 128.8 (**C**(12)H), 127.6 (**C**(11)H), 126.8 (q**C**-9), 125.9 (**C**(13)H), 125.2 (**C**(10)H), 123.2 (q**C**-15), 113.5 (**C**(17)H & **C**(19)H, 108.0 (q**C**-5), 106.8 (q**C**-3), 69.6 (**C**(8)H_2), 55.3

(**C**(21)H_3), 20.3 (**C**(7)H_3); *m/z* (ES+): 321 ($(M+H)^+$ 78%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{17}O_4$ 321.1127; Found 321.1114.

5.5. Suzuki-Miyaura cross-coupling of 3-chloro-4-methoxy-2*H*-chromen-2-one and related heterocycles

General Procedure: A Schlenk tube was heated under vacuum and refilled with N_2 three times. Substrate (1.0 equiv.), boronic acid (1.5 equiv.), $Pd(OAc)_2$ (5 mol%), SPhos (15 mol%) and K_2CO_3 (2.2 equiv.) were added. The Schlenk tube was evacuated and refilled with N_2 three times. Distilled *i*PrOAc (0.03 M) was added *via* syringe. The Schlenk tube was placed in an oil bath preheated to 100 °C. The reaction was stirred at this temperature for 16 h, then cooled to ambient temperature. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (DCM).

4-Methoxy-3-phenyl-2*H*-chromen-2-one (111)[7]



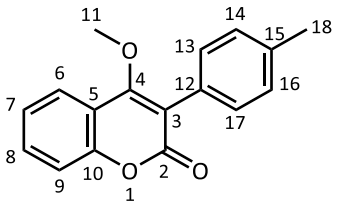
Method 1 (50 mg scale): 3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and phenylboronic acid (43.3 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure to yield **111** as a yellow solid (0.049 g, 82%); m.p. 111–114 °C (lit.[7] 117–119 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.9, 1.3, 1H, ArC**H**), 7.60 – 7.51 (m, 1H, ArC**H**), 7.50 – 7.26 (m, 7H, 7 × ArC**H**), 3.56 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4 (q**C**-4), 162.9 (q**C**-2), 152.5 (q**C**-10), 132.4 (q**C**-12), 132.0 (**C**(8)H), 131.0 (**C**(13)H & **C**(17)H), 128.4 (**C**(15)H), 128.3 (**C**(14)H & **C**(16)H), 124.0 (**C**(7)H), 123.9 (**C**(6)H), 117.8 (q**C**-5), 116.5 (**C**(9)H), 111.1 (q**C**-3), 61.3 (**C**(11)H$_3$); *m/z* (ES+): 253 ($(M+H)^+$ 12%).

Method 2 (1.00 g scale): A 100 mL, 3-neck round-bottomed flask fitted with a condenser and a vacuum/N_2 inlet was heated under vacuum and refilled with N_2 three times. Allowed apparatus to cool to ambient temperature. K_2CO_3 (1.44 g, 10.446 mmol, 2.2 equiv.), $Pd(OAc)_2$ (53 mg, 0.237 mmol, 5 mol%), SPhos (292 mg, 0.712 mmol, 15 mol%), phenylboronic acid (0.87 g, 7.122 mmol, 1.5 equiv.) and 3-chloro-4-methoxy-2*H*-chromen-2-one **104** (1.00 g, 4.478 mmol, 1.0 equiv.) were added under positive pressure of N_2. Distilled *i*PrOAc (50 mL) was added *via* syringe through a rubber septum. The mantle containing the reaction apparatus was heated

to 100 °C. The reaction was stirred at this temperature for 16 h, then cooled to ambient temperature. The reaction mixture was poured onto a pad of celite and the solvent drawn through the celite by suction. The celite was rinsed with EtOAc (2 × 30 mL). The combined organic layers were concentrated under reduced pressure. The residue was dissolved in EtOAc (30 mL) and washed with H_2O (30 mL). The aqueous layer was extracted with EtOAc (30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by recrystallisation from EtOH to give **111** as a yellow solid (1.0022 g, 84%) with identical ^1H and ^{13}C NMR spectra to when the compound was prepared on a 50 mg scale.

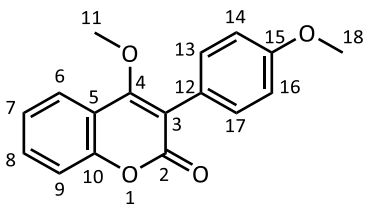
Spectral characteristics were consistent with previously reported data.[7]

4-Methoxy-3-(4-methylphenyl)-2*H*-chromen-2-one (112)



3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and *p*-tolylboronic acid (48.4 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure to yield **112** as a white solid (0.056 g, 89%); m.p. 128–130 °C; IR ν_{max} (film) 1702 (ester C=O stretch), 1608 (alkene C=C stretch), 1571 (aromatic C–C stretch), 1345 (C–O stretch), 1106 (C–O stretch); ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.9, 1.4, 1H, C(6)**H**), 7.54 (ddd, *J* = 8.4, 7.3, 1.6, 1H, C(8)**H**), 7.40 – 7.20 (m, 6H, 6 × ArC**H**), 3.57 (s, 3H, C(11)**H**$_3$), 2.40 (s, 3H, C(18)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6 (q**C**-2), 162.7 (q**C**-4), 152.4 (q**C**-10), 138.3 (q**C**-15), 131.8 (**C**(8)H), 130.8 (**C**(13)H & **C**(17)H), 129.3 (q**C**-12), 129.1 (**C**(14)H & **C**(16)H), 124.0 (**C**(7)H), 123.8 (**C**(6)H), 117.8 (q**C**-5), 116.4 (**C**(9)H), 111.0 (q**C**-3), 61.2 (**C**(11)H_3), 21.4 (**C**(18)H_3); *m/z* (ES+): 267 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{15}O_3$ 267.1021; Found 267.1011.

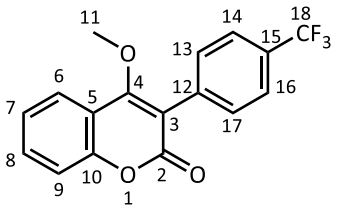
4-Methoxy-3-(4-methoxyphenyl)-2*H*-chromen-2-one (113)



3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and 4-methoxyphenylboronic acid (54.1 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure to yield **113** as a yellow solid

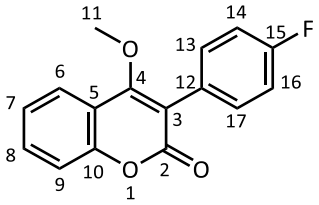
(0.053 g, 79%); m.p. 134–138 °C; IR ν_{max} (film) 1710 (ester C=O stretch), 1606 (alkene C=C stretch), 1512 (aromatic C–C stretch), 1347 (C–O stretch), 1246 (C–O stretch), 1109 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.9, 1.4, 1H, C(6)**H**), 7.60 – 7.47 (m, 1H, C(8)**H**), 7.45 – 7.36 (m, 2H, C(13)**H** & C(17)**H**), 7.36 – 7.24 (m, 2H, C(7)**H** & C(9)**H**), 7.06 – 6.90 (m, 2H, C(14)**H** & C(16)**H**), 3.85 (s, 3H, C(18)$\mathbf{H}_3$), 3.58 (s, 3H, C(11)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (q**C**-2), 162.7 (q**C**-4), 159.6 (q**C**-15), 152.4 (q**C**-10), 132.1 (**C**(13)H & **C**(17)H), 131.8 (**C**(8)H), 124.3 (q**C**-12), 124.0 (**C**(7)H), 123.8 (**C**(6)H), 117.9 (q**C**-5), 116.4 (**C**(9)H), 113.8 (**C**(14)H & **C**(16)H), 111.0 (q**C**-3), 61.1 (**C**(11)H_3), 55.3 (**C**(18)H_3); *m/z* (ES+): 283 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{15}O_4$ 283.0970; Found 283.0970.

4-Methoxy-3-(4-(trifluoromethyl)phenyl)-2*H*-chromen-2-one (114)



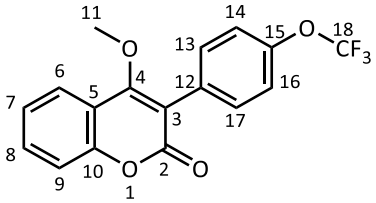
3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and 4-(trifluoromethyl)phenylboronic acid (67.6 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure to yield **114** as a yellow solid (0.058 g, 76%); m.p. 153–156 °C; IR ν_{max} (film) 1700 (ester C=O stretch), 1612 (alkene C=C stretch), 1567 (aromatic C–C stretch), 1327 (C–O stretch), 1121 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.0, 1.5, 1H, C(6)**H**), 7.71 (d, *J* = 8.2, 2H, C(14)**H** & C(16)**H**), 7.67 – 7.53 (m, 3H, C(8)**H**, C(13)**H** & C(17)**H**), 7.41 – 7.28 (m, 2H, C(7)**H** & C(9)**H**), 3.59 (s, 3H, C(11)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (q**C**-4), 162.9 (q**C**-2), 152.6 (q**C**-10), 136.2 (q**C**-12), 132.5 (**C**(8)H), 131.4 (**C**(13)H & **C**(17)H), 130.5 (q, *J* = 32, q**C**-15), 125.2 (q, *J* = 4, **C**(14)H & **C**(16)H), 124.3 (**C**(7)H), 124.0 (**C**(6)H), 124.0 (q, *J* = 272, q**C**-18), 117.4 (q**C**-5), 116.6 (**C**(9)H), 110.2 (q**C**-3), 61.6 (C(11)$\mathbf{H}_3$); ^{19}F NMR (282 MHz, $CDCl_3$) δ -63 (s, C(18)$\mathbf{F}_3$); *m/z* (ES+): 321 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{12}O_3F_3$ 321.0739; Found 321.0735.

4-Methoxy-3-(4-fluorophenyl)-2*H*-chromen-2-one (115)



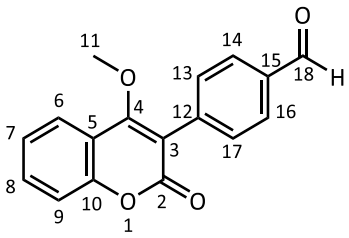
3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and 4-fluorophenylboronic acid (49.8 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure to yield **115** as a yellow solid (0.046 g, 72%); m.p. 135–137 °C; IR ν_{max} (film) 1699 (ester C=O stretch), 1609 (alkene C=C stretch), 1570 (aromatic C–C stretch), 1222 (C–O stretch), 1161 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.9, 1.6, 1H, C(6)**H**), 7.56 (ddd, *J* = 8.4, 7.3, 1.6, 1H, C(8)**H**), 7.51 – 7.41 (m, 2H, C(13)**H** & C(17)**H**), 7.39 – 7.27 (m, 2H, C(7)**H** & C(9)**H**), 7.21 – 7.08 (m, 2H, C(14)**H** & C(16)**H**), 3.58 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (q**C**-4), 163.2 (q**C**-2), 162.6 (d, *J* = 248, q**C**-15), 152.5 (q**C**-10), 132.8 (d, *J* = 8, **C**(13)H & **C**(17)H), 132.2 (**C**(8)H), 128.1 (d, *J* = 4, q**C**-12), 124.1 (**C**(7)H), 123.9 (**C**(6)H), 117.6 (q**C**-5), 116.5 (**C**(9)H), 115.4 (d, *J* = 22, **C**(14)H & **C**(16)H), 110.4 (q**C**-3), 61.3 (**C**(11)H_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -113 (s, C(15)**F**); *m/z* (ES+): 271 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{12}O_3F$ 271.0770; Found 271.0770.

4-Methoxy-3-(4-(trifluoromethoxy)phenyl)-2*H*-chromen-2-one (116)



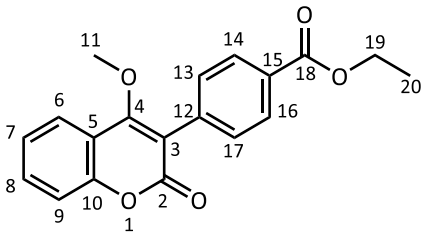
3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and 4-(trifluoromethoxy)phenylboronic acid (73.3 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure to yield **116** as a yellow solid (0.061 g, 77%); m.p. 145–146 °C; IR ν_{max} (film) 1700 (ester C=O stretch), 1616 (alkene C=C stretch), 1570 (aromatic C–C stretch), 1351 (C–O stretch), 1258 (C–O stretch), 1211 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.9, 1.4, 1H, C(6)**H**), 7.62 – 7.48 (m, 3H, 3 × ArC**H**), 7.41 – 7.27 (m, 4H, 4 × ArC**H**), 3.59 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5 (q**C**-4), 163.1 (q**C**-2), 152.6 (q**C**-10), 149.1 (q, *J* = 2, q**C**-15), 132.5 (**C**(13)H & **C**(17)H), 132.3 (**C**(8)H), 130.9 (q**C**-12), 124.2 (**C**(7)H), 123.9 (**C**(6)H), 120.6 (**C**(14)H & **C**(16)H), 120.5 (q, *J* = 258, q**C**-18), 117.5 (q**C**-5), 116.6 (**C**(9)H), 110.2 (q**C**-3), 61.4 (**C**(11)H_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -58 (s, C(18)**F**$_3$); *m/z* (ES+): 337 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ $C_{17}H_{12}O_4F_3$ 337.0688; Found 337.0671.

4-(4-Methoxy-2-oxo-2*H*-chromen-3-yl)benzaldehyde (117)



3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and 4-formylphenylboronic acid (53.4 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure. The residue was purified by column chromatography (MeOH:DCM 1:99) to yield **117** as a yellow solid (0.032 g, 48%); m.p. 154–155 °C; IR ν_{max} (film) 2729 (aldehyde C–H stretch), 1701 (ester C=O stretch), 1607 (alkene C=C stretch), 1567 (aromatic C–C stretch), 1348 (C–O stretch), 1207 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.07 (s, 1H, C(18)**H**), 8.02 – 7.93 (m, 2H, C(14)**H** & C(16)**H**), 7.89 (dd, *J* = 8.0, 1.3, 1H, C(6)**H**), 7.74 – 7.65 (m, 2H, C(13)**H** & C(17)**H**), 7.64 – 7.53 (m, 1H, C(8)**H**), 7.42 – 7.28 (m, 2H, C(7)**H** & C(9)**H**), 3.60 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7 (**C**(18)H), 163.8 (q**C**-4), 162.7 (q**C**-2), 152.7 (q**C**-10), 138.9 (q**C**-12), 136.0 (q**C**-15), 132.6 (**C**(8)H), 131.8 (**C**(13)H & **C**(17)H), 129.5 (**C**(14)H & **C**(16)H), 124.3 (**C**(7)H), 124.0 (**C**(6)H), 117.4 (q**C**-5), 116.6 (**C**(9)H), 110.3 (q**C**-3), 61.7 (**C**(11)H_3); *m/z* (ES+): 281 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{13}O_4$ 281.0814; Found 281.0815.

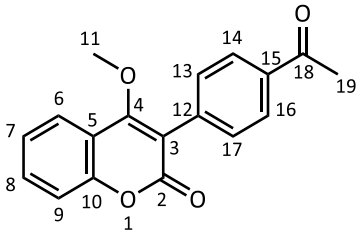
Ethyl 4-(4-methoxy-2-oxo-2*H*-chromen-3-yl)benzoate (118)



3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and 4-ethoxycarbonylbenzeneboronic acid (69.1 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure to yield **118** as an off-white solid (0.070 g, 91%); m.p. 131–133 °C; IR ν_{max} (film) 1715 (ester C=O stretch), 1610 (alkene C=C stretch), 1573 (aromatic C–C stretch), 1348 (C–O stretch), 1274 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 – 8.07 (m, 2H, C(14)**H** & C(16)**H**), 7.88 (dd, *J* = 8.0, 1.3, 1H, C(6)**H**), 7.64 – 7.52 (m, 3H, C(8)**H**, C(13)**H** & C(17)**H**), 7.41 – 7.28 (m, 2H, C(7)**H** & C(9)**H**), 4.41 (q, *J* = 7.1, 2H, C(19)**H**$_2$), 3.57 (s, 3H, C(11)**H**$_3$), 1.41 (t, *J* = 7.1, 3H, C(20)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2 (q**C**-18), 163.5 (q**C**-4), 162.9 (q**C**-2), 152.6 (q**C**-10), 137.2 (q**C**-12), 132.4 (**C**(8)H), 131.1 (**C**(13)H & **C**(17)H), 130.4 (q**C**-15), 129.4 (**C**(14)H & **C**(16)H), 124.2 (**C**(7)H), 124.0 (**C**(6)H), 117.5 (q**C**-5), 116.6 (**C**(9)H), 110.4 (q**C**-3), 61.5

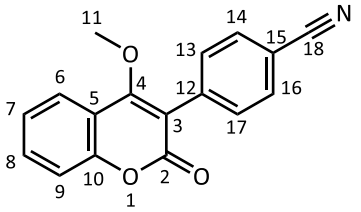
(**C**(11)H_3), 61.1 (**C**(19)H_2), 14.3 (**C**(20)H_3); *m/z* (ES+): 325 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{17}O_5$ 325.1076; Found 325.1079.

3-(4-Acetylphenyl)-4-methoxy-2*H*-chromen-2-one (119)



3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and 4-acetylphenylboronic acid (58.4 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure to yield **119** as a white solid (0.053 g, 76%); m.p. 183–187 °C; IR ν_{max} (film) 1712 (ester C=O stretch), 1682 (ketone C=O stretch), 1611 (alkene C=C stretch), 1571 (aromatic C–C stretch), 1347 (C–O stretch), 1267 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 – 7.99 (m, 2H, C(14)**H** & C(16)**H**), 7.89 (dd, *J* = 7.9, 1.5, 1H, C(6)**H**), 7.65 – 7.52 (m, 3H, 3 × ArC**H**), 7.41 – 7.28 (m, 2H, 2 × ArC**H**), 3.59 (s, 3H, C(11)**H**$_3$), 2.65 (s, 3H, C(19)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6 (q**C**-18), 163.6 (q**C**-4), 162.9 (q**C**-2), 152.6 (q**C**-10), 137.5 (q**C**-12), 136.8 (q**C**-15), 132.5 (**C**(8)H), 131.3 (**C**(13)H & **C**(17)H), 128.2 (**C**(14)H & **C**(16)H), 124.2 (**C**(7)H), 124.0 (**C**(6)H), 117.5 (q**C**-5), 116.6 (**C**(9)H), 110.3 (q**C**-3), 61.6 (**C**(11)H_3), 26.7 (**C**(19)H_3); *m/z* (ES+): 295 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{15}O_4$ 295.0970; Found 295.0952.

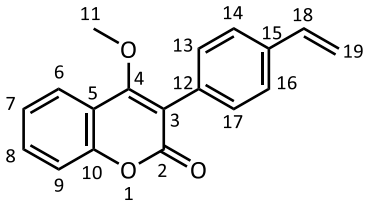
4-(4-Methoxy-2-oxo-2*H*-chromen-3-yl)benzonitrile (120)



3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and 4-cyanophenylboronic acid (52.3 mg, 0.356 mmol, 1.5 equiv were used in the General Procedure to yield **120** as a white solid (0.055 g, 84%); m.p. 199–202 °C; IR ν_{max} (film) 2225 (C≡N stretch), 1699 (ester C=O stretch), 1610 (alkene C=C stretch), 1454 (aromatic C–C stretch), 1351 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.0, 1.3, 1H, C(6)**H**), 7.79 – 7.71 (m, 2H, C(14)**H** & C(16)**H**), 7.68 – 7.56 (m, 3H, C(8)**H**, C(13)**H** & C(17)**H**), 7.41 – 7.30 (m, 2H, C(7)**H** & C(9)**H**), 3.60 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1 (q**C**-4), 162.5 (q**C**-2), 152.7 (q**C**-10), 137.4 (q**C**-12), 132.8 (**C**(8)H), 132.0 (**C**(14)H & **C**(16)H), 131.8 (**C**(13)H & **C**(17)H), 124.4 (**C**(7)H), 124.1 (**C**(6)H)), 118.5 (q**C**-18), 117.2 (q**C**-5), 116.7 (**C**(9)H),

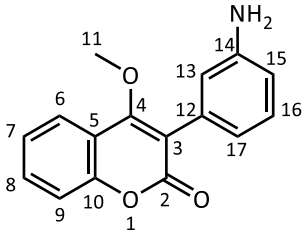
112.2 (q**C**-15), 110.0 (q**C**-3), 61.8 (**C**(11)H_3); *m/z* (ES+): 278 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{17}H_{12}NO_3$ 278.0817; Found 278.0808.

4-Methoxy-3-(4-vinylphenyl)-2*H*-chromen-2-one (121)



3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and (4-vinylphenyl)boronic acid (52.7 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure to yield **121** as an yellow solid (0.051 g, 77%); m.p. 102–104 °C; IR ν_{max} (film) 1713 (ester C=O stretch), 1608 (alkene C=C stretch), 1571 (aromatic C–C stretch), 1346 (C–O stretch), 1328 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.82 (m, 1H, C(6)**H**), 7.60 – 7.41 (m, 5H, 5 × ArC**H**), 7.39 – 7.26 (m, 2H, 2 × ArC**H**), 6.76 (dd, *J* = 17.6, 10.9, 1H, C(18)**H**), 5.81 (dd, *J* = 17.6, 0.8, 1H, C(19)$\mathbf{H}_2$), 5.30 (dd, *J* = 10.9, 0.8, 1H, C(19)$\mathbf{H}_2$), 3.59 (s, 3H, C(11)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (q**C**-4), 163.0 (q**C**-2), 152.5 (q**C**-10), 137.7 (q**C**-12), 136.4 (**C**(18)H), 132.0 (**C**(8)H), 131.7 (q**C**-15), 131.1 (**C**(13)H & **C**(17)H), 126.1 (**C**(14)H & **C**(16)H), 124.1 (**C**(7)H), 123.9 (**C**(6)H), 117.7 (q**C**-5), 116.5 (**C**(9)H), 114.6 (**C**(19)H_2), 110.9 (q**C**-3), 61.3 (**C**(11)H_3); *m/z* (ES+): 279 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{18}H_{15}O_3$ 279.1021; Found 279.1025.

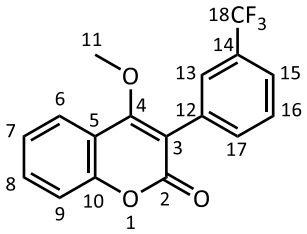
3-(3-Aminophenyl)-4-methoxy-2*H*-chromen-2-one (122)



3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and 3-aminophenylboronic acid monohydrate (55.2 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure to yield **122** as an orange solid (0.050 g, 79%); m.p. 131–136 °C; IR ν_{max} (film) 3367 (N–H stretch), 1712 (ester C=O stretch), 1645 (N–H bend), 1610 (alkene C=C stretch), 1570 (aromatic C–C stretch), 1266 (C–O stretch), 738 (N–H wag); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 – 7.81 (m, 1H, C(6)**H**), 7.53 (ddd, *J* = 8.4, 7.3, 1.6, 1H, C(8)**H**), 7.38 – 7.14 (m, 3H, C(7)**H**, C(9)**H** & C(16)**H**), 6.86 – 6.76 (m, 2H, C(13)**H** & C(17)**H**), 6.71 (ddd, *J* = 8.0, 2.4, 1.0, 1H, C(15)**H**), 3.63 (s, 3H, C(11)$\mathbf{H}_3$), 3.53 (br s, 2H, N$\mathbf{H}_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5 (q**C**-4), 162.6 (q**C**-2), 152.4 (q**C**-10), 146.4 (q**C**-14), 133.3 (q**C**-12), 131.9

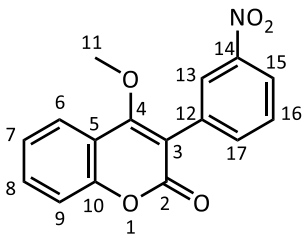
(**C**(8)H), 129.2 (**C**(7)H), 124.0 (**C**(16)H), 123.9 (**C**(6)H), 121.5 (**C**(17)H), 117.8 (q**C**-5), 117.7 (**C**(15)H), 116.4 (**C**(9)H), 115.4 (**C**(13)H), 110.8 (q**C**-3), 61.1 (**C**(11)H_3); *m/z* (ES+): 268 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{14}NO_3$ 268.0974; Found 268.0961.

4-Methoxy-3-(3-(trifluoromethyl)phenyl)-2*H*-chromen-2-one (123)



3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and 3-(trifluoromethyl)phenylboronic acid (67.6 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure to yield **123** as a yellow solid (0.066 g, 87%); m.p. 95–97 °C; IR ν_{max} (film) 1716 (ester C=O stretch), 1610 (alkene C=C stretch), 1570 (aromatic C–C stretch), 1330 (C–O stretch), 1125 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 – 7.84 (m, 1H, C(6)**H**), 7.79 – 7.53 (m, 5H, 5 × ArC**H**), 7.40 – 7.28 (m, 2H, 2 × ArC**H**), 3.57 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (q**C**-4), 162.9 (q**C**-2), 152.6 (q**C**-10), 134.4 (**C**(17)H), 133.2 (q**C**-12), 132.5 (**C**(8)H), 130.8 (q, *J* = 33, q**C**-14), 128.8 (**C**(16)H), 127.8 (q, *J* = 4, **C**(15)H), 125.2 (q, *J* = 4, **C**(13)H), 124.3 (**C**(7)H), 124.0 (**C**(6)H), 124.0 (q, *J* = 273, q**C**-18), 117.4 (q**C**-5), 116.6 (**C**(9)H), 110.1 (q**C**-3), 61.6 (**C**(11)H_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -63 (s, C(18)**F**$_3$); *m/z* (ES+): 321 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{12}O_3F_3$ 321.0739; Found 321.0734.

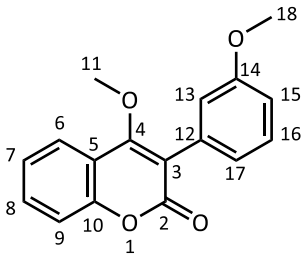
4-Methoxy-3-(3-nitrophenyl)-2*H*-chromen-2-one (124)



3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and 3-nitrophenylboronic acid (59.4 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure to yield **124** as a yellow solid (0.058 g, 82%); m.p. 153–155 °C; IR ν_{max} (film) 1714 (ester C=O stretch), 1611 (alkene C=C stretch), 1570 (aromatic C–C stretch), 1528 (asymmetric N–O stretch), 1349 (symmetric N–O stretch), 1298 (C–O stretch), 1106 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (t, *J* = 1.9, 1H, C(13)**H**), 8.26 (ddd, *J* = 8.3, 2.3, 1.1, 1H, C(15)**H**), 7.95 – 7.82 (m, 2H, C(6)**H** & C(17)**H**), 7.69 – 7.57 (m, 2H, C(8)**H** & C(16)**H**), 7.42 – 7.31 (m, 2H, C(7)**H** & C(9)**H**), 3.62 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2 (q**C**-4),

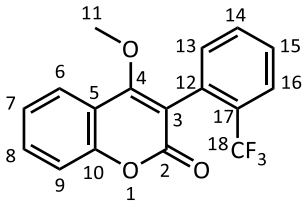
162.7 (q**C**-2), 152.7 (q**C**-10), 148.2 (q**C**-14), 137.1 (**C**(17)H), 134.1 (q**C**-12), 132.8 (**C**(16)H), 129.3 (**C**(8)H), 125.9 (**C**(13)H), 124.5 (**C**(7)H), 124.1 (**C**(6)H), 123.3 (**C**(15)H), 117.2 (q**C**-5), 116.7 (**C**(9)H), 109.6 (q**C**-3), 61.9 (**C**(11)H_3); *m/z* (ES+): 298 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{12}NO_5$ 298.0715; Found 298.0720.

4-Methoxy-3-(3-methoxyphenyl)-2*H*-chromen-2-one (125)



3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and 3-methoxyphenylboronic acid (54.1 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure to yield **125** as a yellow oil (0.061 g, 91%); IR ν_{max} (film) 1715 (ester C=O stretch), 1611 (alkene C=C stretch), 1572 (aromatic C–C stretch), 1347 (C–O stretch), 1214 (C–O stretch), 1106 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.9, 1.4, 1H, C(6)**H**), 7.55 (ddd, *J* = 8.6, 7.4, 1.6, 1H, C(8)**H**), 7.44 – 7.22 (m, 3H, 3 × ArC**H**), 7.10 – 6.87 (m, 3H, 3 × ArC**H**), 3.83 (s, 3H, C(18)**H**$_3$), 3.60 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (q**C**-2), 162.8 (q**C**-4), 159.4 (q**C**-14), 152.5 (q**C**-10), 133.7 (q**C**-12), 132.0 (**C**(8)H), 129.3 (**C**(16)H), 124.0 (**C**(7)H), 123.9 (**C**(6)H), 123.5 (**C**(17)H), 117.7 (q**C**-5), 116.6 (**C**(15)H), 116.4 (**C**(9)H), 114.1 (**C**(13)H), 110.7 (q**C**-3), 61.1 (**C**(11)H_3), 55.3 (**C**(18)H_3); *m/z* (ES+): 283 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{15}O_4$ 283.0970; Found 283.0961.

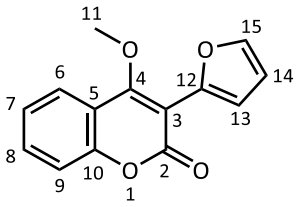
4-Methoxy-3-(2-(trifluoromethyl)phenyl)-2*H*-chromen-2-one (126)



3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and 2-(trifluoromethyl)phenylboronic acid (67.6 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure to yield **126** as a yellow solid (0.042 g, 56%); IR ν_{max} (film) 1716 (ester C=O stretch), 1613 (alkene C=C stretch), 1573 (aromatic C–C stretch), 1350 (C–O stretch), 1315 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.0, 1.3, 1H, C(13)**H**), 7.82 – 7.74 (m, 1H, C(16)**H**), 7.68 – 7.45 (m, 4H, C(6)**H**, C(7)**H**, C(8)**H** & C(15)**H**), 7.41 – 7.27 (m, 2H, C(9)**H** & C(14)**H**), 3.56 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.0 (q**C**-4), 161.5 (q**C**-2), 152.6 (q**C**-10), 133.7 (**C**(8)H), 132.5 (q, *J* = 29, q**C**-12), 132.3 (**C**(7)H),

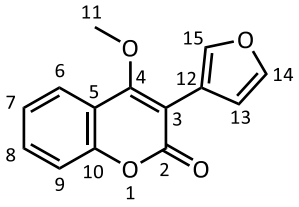
131.7 (**C**(6)H), 130.7 (q, *J* = 30, q**C**-17), 129.2 (**C**(15)H), 126.6 (q, *J* = 5, **C**(16)H), 124.2 (**C**(13)H), 124.1 (**C**(14)H), 123.9 (d, *J* = 274, q**C**-18), 116.9 (q**C**-5), 116.6 (**C**(9)H), 105.7 (q**C**-3), 60.3 (**C**(11)H_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ -61 (s, C(18)**F**$_3$); *m/z* (ES+): 321 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{12}O_3F_3$ 321.0739; Found 321.0726.

3-(Furan-2-yl)-4-methoxy-2*H*-chromen-2-one (127)



3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and 2-furanylboronic acid (39.8 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure to yield **127** as a yellow oil (0.039 g, 68%); IR ν_{max} (film) 1723 (ester C=O stretch), 1625 (C=C stretch), 1610 (C=C stretch), 1549 (aromatic C–C stretch), 1348 (C–O stretch), 1328 (C–O stretch), 1124 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, 1H, *J* = 8.0, 1.4, C(6)**H**), 7.61 – 7.51 (m, 2H, C(8)**H** & C(15)**H**), 7.37 – 7.27 (m, 2H, C(7)**H** & C(9)**H**), 6.82 (dd, *J* = 3.3, 0.8, 1H, C(13)**H**), 6.55 (dd, *J* = 3.3, 1.9, 1H, C(14)**H**), 3.80 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9 (q**C**-4), 161.9 (q**C**-2), 152.4 (q**C**-10), 144.5 (q**C**-12), 142.9 (**C**(13)H), 132.5 (**C**(8)H), 124.2 (**C**(6)H), 124.0 (**C**(7)H), 117.3 (q**C**-5), 116.6 (**C**(9)H), 113.9 (**C**(15)H), 111.6 (**C**(14)H), 101.4 (q**C**-3), 60.5 (**C**(11)H_3); *m/z* (ES+): 243 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{11}O_4$ 243.0657; Found 243.0652.

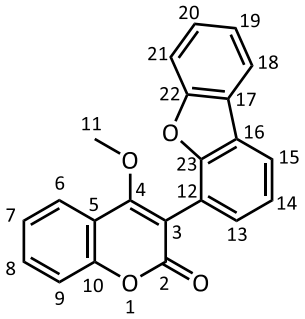
3-(Furan-3-yl)-4-methoxy-2*H*-chromen-2-one (128)



3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and 3-furanylboronic acid (39.8 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure. The residue was purified by column chromatography (EtOAc:hexanes 10:90) to yield **128** as a white solid (0.037 g, 64%); m.p. 97–99 °C; IR ν_{max} (film) 1710 (ester C=O stretch), 1614 (C=C stretch), 1602 (C=C stretch), 1538 (aromatic C–C stretch), 1329 (C–O stretch), 1161 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 0.6, 1H, C(15)**H**), 7.80 (dd, *J* = 7.9, 1.4, 1H, C(6)**H**), 7.63 – 7.45 (m, C(7)**H** & C(8)**H**), 7.42 – 7.28 (m, 2H, C(9)**H** & C(14)**H**), 7.10 – 6.92 (m, 1H, C(13)**H**), 3.87 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7 (q**C**-4), 162.1

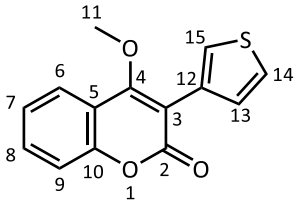
(q**C**-2), 152.2 (q**C**-10), 144.3 (**C**(14)H), 142.5 (**C**(15)H), 131.7 (**C**(8)H), 124.3 (**C**(6)H), 123.4 (**C**(7)H), 117.5 (q**C**-5), 116.6 (**C**(9)H), 115.8 (q**C**-12), 111.2 (**C**(13)H), 108.1 (q**C**-3), 60.8 (**C**(11)H_3); *m/z* (ES+): 243 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{11}O_4$ 243.0657; Found 243.0656.

3-(Dibenzo[*b*,*d*]furan-4-yl)-4-methoxy-2*H*-chromen-2-one (129)



3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and dibenzofuran-4-boronic acid (75.5 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure to yield **129** as a yellow solid (0.068 g, 84%); m.p. 196–198 °C; IR ν_{max} (film) 1714 (ester C=O stretch), 1645 (C=C stretch), 1570 (aromatic C–C stretch), 1349 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 – 7.90 (m, 3H, 3 × ArC**H**), 7.64 – 7.49 (m, 3H, 3 × ArC**H**), 7.49 – 7.29 (m, 5H, 5 × ArC**H**), 3.50 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (q**C**-4), 162.8 (q**C**-2), 156.2 (q**C**-10), 154.7 (q**C**-Ar), 152.7 (q**C**-Ar), 132.3 (Ar**C**H), 130.0 (Ar**C**H), 127.4 (Ar**C**H), 124.5 (q**C**-Ar), 124.2 (q**C**-Ar), 124.1 (Ar**C**H), 124.1 (Ar**C**H), 123.0 (Ar**C**H), 122.8 (Ar**C**H), 121.2 (Ar**C**H), 120.8 (Ar**C**H), 117.6 (q**C**-Ar), 117.3 (q**C**-5), 116.6 (**C**(9)H), 112.0 (Ar**C**H), 104.3 (q**C**-3), 60.6 (**C**(11)H_3); *m/z* (ES+): 343 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{15}O_4$ 343.0970; Found 343.0960.

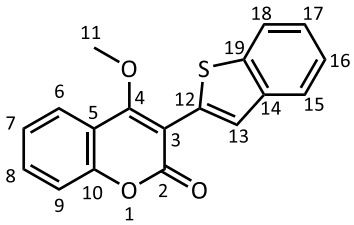
4-Methoxy-3-(thiophen-3-yl)-2*H*-chromen-2-one (130)



3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and 3-thiophenylboronic acid (45.6 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure to yield **130** as a yellow oil (0.057 g, 93%); IR ν_{max} (film) 1717 (ester C=O stretch), 1610 (C=C stretch), 1573 (aromatic C–C stretch), 1341 (C–O stretch), 1326 (C–O stretch), 756 (C–S stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 7.9, 1.6, 1H, C(6)**H**), 7.68 – 7.63 (m, 1H, C(14)**H**), 7.54 (ddd, *J* = 8.7, 7.3, 1.6, 1H, C(8)**H**), 7.43 – 7.27 (m, 4H, 4 × ArC**H**), 3.66 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4 (q**C**-4), 162.8 (q**C**-2), 152.3 (q**C**-10), 132.0 (**C**(8)H), 131.2 (q**C**-12), 129.6 (**C**(13)H), 126.9 (**C**(14)H), 124.9 (**C**(15)H), 124.2 (**C**(6)H), 123.8 (**C**(7)H), 117.7 (q**C**-5),

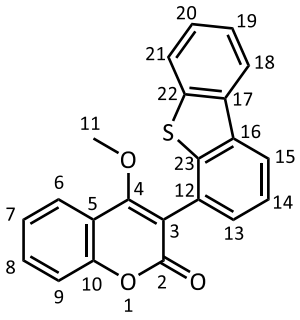
116.5 (**C**(9)H), 107.9 (q**C**-3), 60.8 (**C**(11)H_3); *m/z* (ES+): 259 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{14}H_{11}O_3S$ 259.0429; Found 259.0432.

3-(Benzo[*b*]thiophen-2-yl)-4-methoxy-2*H*-chromen-2-one (131)



3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and benzo[*b*]thiophene-2-boronic acid (63.4 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure to yield **131** as a yellow solid (0.055 g, 75%); m.p. 132–136 °C; IR ν_{max} (film) 1720 (ester C=O stretch), 1608 (C=C stretch), 1554 (aromatic C–C stretch), 1351 (C–O stretch), 1328 (C–O stretch), 749 (C–S stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 0.6, 1H, C(13)**H**), 7.90 – 7.75 (m, 3H, C(6)**H**, C(16)**H** & C(17)**H**), 7.57 (ddd, *J* = 8.4, 7.3, 1.6, 1H, C(8)**H**), 7.41 – 7.28 (m, 4H, C(7)**H**, C(9)**H**, C(15)**H** & C(18)**H**), 3.90 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8 (q**C**-4), 161.8 (q**C**-2), 152.4 (q**C**-10), 140.9 (q**C**-19), 139.1 (q**C**-14), 132.6 (q**C**-12), 132.5 (Ar**C**H), 127.6 (Ar**C**H), 125.0 (Ar**C**H), 124.4 (Ar**C**H), 124.4 (Ar**C**H), 124.1 (Ar**C**H), 124.0 (Ar**C**H), 121.9 (Ar**C**H), 117.2 (q**C**-5), 116.7 (**C**(9)H), 107.8 (q**C**-3), 61.3 (**C**(11)H_3); *m/z* (ES+): 309 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{18}H_{13}O_3S$ 309.0585; Found 309.0590.

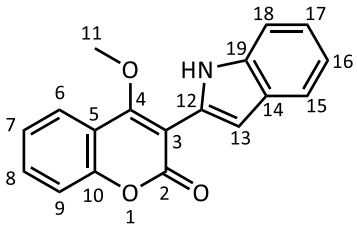
3-(Dibenzo[*b*,*d*]thiophen-4-yl)-4-methoxy-2*H*-chromen-2-one (132)



3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and dibenzothiophene-4-boronic acid (81.2 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure to yield **132** as a yellow solid (0.084 g, 99%); m.p. 191–196 °C; IR ν_{max} (film) 1714 (ester C=O stretch), 1611 (C=C stretch), 1566 (aromatic C–C stretch), 1349 (C–O stretch), 754 (C–S stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 – 8.12 (m, 2H, C(15)**H** & C(18)**H**), 7.94 (dd, *J* = 8.0, 1.5, 1H, ArC**H**), 7.86 – 7.75 (m, 1H, C(6)**H**), 7.65 – 7.28 (m, 7H, 7 × ArC**H**), 3.50 (s, 3H, C(11)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2 (q**C**-4), 162.5 (q**C**-2), 152.7 (q**C**-10), 141.7 (q**C**-23), 139.4 (q**C**-22), 135.8 (q**C**-Ar), 135.8 (q**C**-Ar), 132.4 (Ar**C**H), 129.8 (Ar**C**H), 127.9 (q**C**-12), 127.0 (Ar**C**H), 124.7 (Ar**C**H), 124.6 (Ar**C**H), 124.2 (Ar**C**H), 124.1 (Ar**C**H), 122.9 (Ar**C**H), 121.9 (Ar**C**H), 121.8 (Ar**C**H), 117.3

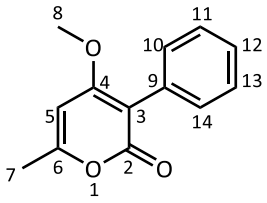
(q**C**-5), 116.6 (**C**(9)H), 107.1 (q**C**-3), 60.3 (**C**(11)H_3); *m/z* (ES+): 359 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{22}H_{15}O_3S$ 359.0742; Found 359.0746.

3-(1*H*-Indol-2-yl)-4-methoxy-2*H*-chromen-2-one (133)



3-Chloro-4-methoxy-2*H*-chromen-2-one **104** (50.0 mg, 0.237 mmol, 1.0 equiv.) and (1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl)boronic acid (92.9 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure to yield **133** as a yellow solid (0.038 g, 55%); m.p. 169–174 °C; IR ν_{max} (film) 3403 (N–H stretch), 1645 (ester C=O stretch), 1454 (aromatic C–C stretch), 1346 (C–O stretch), 1266 (C–N stretch), 1112 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.43 (br s, 1H, N–**H**), 7.89 – 7.81 (m, 1H, C(6)**H**), 7.67 (dd, *J* = 7.9, 0.9, 1H, C(18)**H**), 7.60 – 7.52 (m, 1H, C(8)**H**), 7.45 (dd, *J* = 8.1, 0.9, 1H, C(15)**H**), 7.42 – 7.28 (m, 3H, C(7)**H**, C(9)**H** & C(13)**H**), 7.23 (ddd, *J* = 8.2, 7.0, 1.2, 1H, C(16)**H**), 7.13 (ddd, *J* = 8.0, 7.0, 1.0, 1H, C(17)**H**), 3.98 (s, 3H, C(11)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4 (q**C**-4), 163.0 (q**C**-2), 152.0 (q**C**-10), 135.6 (q**C**-19), 132.0 (**C**(8)H), 128.2 (q**C**-14), 128.1 (q**C**-12), 124.7 (**C**(7)H), 123.7 (**C**(6)H), 123.1 (**C**(16)H), 120.8 (**C**(18)H), 120.1 (**C**(17)H), 117.6 (q**C**-5), 116.7 (**C**(9)H), 111.4 (**C**(15)H), 108.1 (q**C**-3), 106.6 (**C**(13)H), 60.5 (**C**(11)H_3); *m/z* (ES+): 292 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{18}H_{14}NO_3$ 292.0974; Found 292.0979.

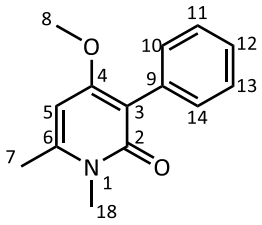
4-Methoxy-6-methyl-3-phenyl-2*H*-pyran-2-one (134)[51]



3-Chloro-4-methoxy-6-methyl-2*H*-pyran-2-one **107** (30.0 mg, 0.172 mmol, 1.0 equiv.) and phenylboronic acid (31.5 mg, 0.258 mmol, 1.5 equiv.) were used in the General Procedure. The residue was purified by column chromatography (EtOAc:hexanes 50:50) to yield **134** as a yellow solid (0.028 g, 75%); m.p. 155–159 °C (lit.[51] 156-157 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.33 (m, 4H, 4 × ArC**H**), 7.32 – 7.24 (m, 1H, ArC**H**), 6.13 (d, *J* = 0.8, 1H, C(5)**H**), 3.82 (s, 3H, C(8)$\mathbf{H}_3$), 2.32 (d, *J* = 0.8, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9 (q**C**-4), 164.3 (q**C**-6), 162.7 (q**C**-2), 131.4 (q**C**-9), 130.5 (**C**(10)H & **C**(14)H), 127.9 (**C**(11)H & **C**(13)H), 127.4 (**C**(12)H), 105.3 (**C**(5)H), 95.3 (q**C**-3), 56.5 (**C**(8)H_3), 20.5 (**C**(7)H_3); *m/z* (ES+): 217 ((M+H)$^+$ 22%).

Spectral characteristics were consistent with previously reported data.[51]

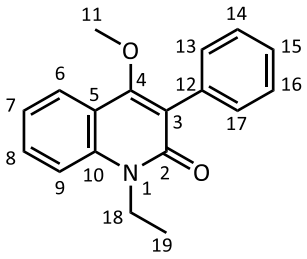
4-Methoxy-1,6-dimethyl-3-phenylpyridin-2(1*H*)-one (135)[52]



3-Chloro-4-methoxy-1,6-dimethylpyridin-2(1*H*)-one **101** (44.5 mg, 0.237 mmol, 1.0 equiv.) and phenylboronic acid (43.3 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure. The residue was purified by column chromatography (MeOH:DCM 0.5:99.5) to yield **135** as a yellow semi-solid (0.052 g, 96%); IR ν_{max} (film) 1634 (amide C=O stretch), 1558 (alkene C=C stretch), 1362 (C–O stretch), 1266 (C–N stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.20 (m, 5H, 5 × ArC**H**), 6.02 (d, *J* = 0.5, 1H, C(5)**H**), 3.75 (s, 3H, C(8)**H**$_3$), 3.54 (s, 3H, C(18)**H**$_3$), 2.40 (d, *J* = 0.6 Hz, 3H, C(7)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (q**C**-4), 162.8 (q**C**-2), 146.1 (q**C**-6), 133.6 (q**C**-9), 130.8 (**C**(10)H & **C**(14)H), 127.7 (**C**(11)H & **C**(13)H), 126.8 (**C**(12)H), 111.8 (q**C**-3), 95.3 (**C**(5)H), 55.8 (**C**(8)H_3), 31.4 (**C**(18)H_3), 21.6 (**C**(7)H_3); *m/z* (ES+): 230 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{16}NO_2$ 230.1181; Found 230.1180.

Spectral characteristics were consistent with previously reported data.[52]

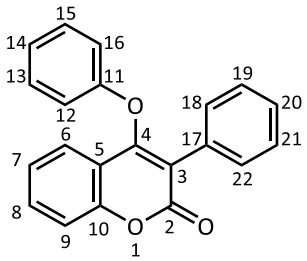
1-Ethyl-4-methoxy-3-phenylquinolin-2(1*H*)-one (136)



3-Chloro-1-ethyl-4-methoxyquinolin-2(1*H*)-one **103** (56.3 mg, 0.237 mmol, 1.0 equiv.) and phenylboronic acid (43.3 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure. The residue was purified by column chromatography (EtOAc:hexanes 10:90) to yield **136** as a clear colourless oil (0.059 g, 89%); IR ν_{max} (film) 1635 (amide C=O stretch), 1593 (alkene C=C stretch), 1356 (C–O stretch), 1111 (C–N stretch); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.0, 1.3, 1H, ArC**H**), 7.66 – 7.56 (m, 1H, ArC**H**), 7.55 – 7.48 (m, 2H, 2 × ArC**H**), 7.48 – 7.31 (m, 4H, 4 × ArC**H**), 7.30 – 7.20 (m, 1H, 1 × ArC**H**), 4.39 (q, *J* = 7.1, 2H, C(18)**H**$_2$), 3.50 (s, 3H, C(11)**H**$_3$), 1.38 (t, *J* = 7.1, 3H, C(19)**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9 (q**C**-4), 160.4 (q**C**-2), 138.4 (q**C**-10), 133.5 (q**C**-12), 130.9 (Ar**C**H), 130.9 (2 × Ar**C**H), 128.1 (2 × Ar**C**H), 127.7 (Ar**C**H), 124.4 (Ar**C**H), 121.7 (Ar**C**H), 119.3 (q**C**-5), 118.5 (q**C**-3), 113.8 (Ar**C**H), 60.8 (C(11)**H**$_3$), 37.8 (C(18)**H**$_2$), 12.8

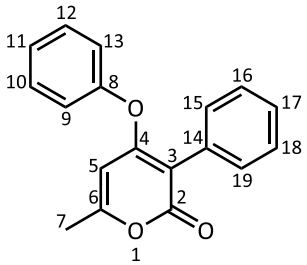
(**C**(19)H_3); *m/z* (ES+): 280 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{18}H_{18}NO_2$ 280.1338; Found 280.1335.

4-Phenoxy-3-phenyl-2*H*-chromen-2-one (137)



3-Chloro-4-phenoxy-2*H*-chromen-2-one **105** (64.6 mg, 0.237 mmol, 1.0 equiv.) and phenylboronic acid (43.3 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure. The residue was purified by column chromatography (EtOAc:hexanes 10:90) to yield **137** as a white solid (0.063 g, 85%); m.p. 191–194 °C; IR ν_{max} (film) 1723 (ester C=O stretch), 1625 (C=C stretch), 1483 (aromatic C–C stretch), 1350 (C–O stretch), 1207 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 8.0, 1.5, 1H, ArC**H**), 7.56 (ddd, *J* = 8.8, 7.3, 1.6, 1H, ArC**H**), 7.47 – 7.32 (m, 3H, 3 × ArC**H**), 7.31 – 7.10 (m, 6H, 6 × ArC**H**), 7.00 – 6.90 (m, 1H, ArC**H**), 6.84 – 6.75 (m, 2H, 2 × ArC**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (q**C**-2), 158.6 (q**C**-4), 156.5 (q**C**-11), 153.1 (q**C**-10), 132.3 (Ar**C**H), 130.4 (q**C**-17), 130.1 (2 × Ar**C**H), 129.7 (2 × Ar**C**H), 128.4 (Ar**C**H), 128.0 (2 × Ar**C**H), 124.4 (Ar**C**H), 124.3 (Ar**C**H), 123.2 (Ar**C**H), 118.3 (q**C**-5), 117.0 (q**C**-3), 116.8 (Ar**C**H), 116.3 (2 × Ar**C**H); *m/z* (ES+): 315 ((M+H)$^+$ 100%); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for $C_{21}H_{15}O_3$ 315.1021; Found 315.1013.

6-Methyl-4-phenoxy-3-phenyl-2*H*-pyran-2-one (138)

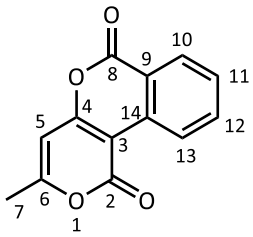


3-Chloro-6-methyl-4-phenoxy-2*H*-pyran-2-one **109** (56.1 mg, 0.237 mmol, 1.0 equiv.) and phenylboronic acid (43.3 mg, 0.356 mmol, 1.5 equiv.) were used in the General Procedure. The residue was purified by column chromatography (EtOAc:hexanes 8:92) to yield **138** as an off-white solid (0.050 g, 76%); m.p. 129–133 °C; IR ν_{max} (film) 1716 (ester C=O stretch), 1647 (C=C stretch), 1566 (C=C stretch), 1489 (aromatic C–C stretch), 1345 (C–O stretch), 1220 (C–O stretch); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.50 (m, 2H, 2 × ArC**H**), 7.44 – 7.33 (m, 4H, 4 × ArC**H**), 7.33 – 7.19 (m, 2H, 2 × ArC**H**), 7.07 – 6.98 (m, 2H, 2 × ArC**H**), 5.72 (d, *J* = 0.8, 1H, C(5)**H**), 2.20 (d, *J* = 0.8, 3H, C(7)**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2 (q**C**-6), 163.9 (q**C**-2), 162.1 (q**C**-4), 153.7 (q**C**-8), 130.8

(q**C**-14), 130.4 (2 × Ar**C**H), 130.2 (2 × Ar**C**H), 128.0 (2 × Ar**C**H), 127.8 (Ar**C**H), 125.6 (Ar**C**H), 120.5 (2 × Ar**C**H), 108.7 (q**C**-3), 98.4 (**C**(5)H), 20.2 (**C**(7)H_3); *m/z* (ES+): 279 ($(M+H)^+$ 100%); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{15}O_3$ 279.1021; Found 279.1018.

5.6. Oxidation of 3-methylpyrano[4,3-*c*]isochromen-1(6*H*)-one

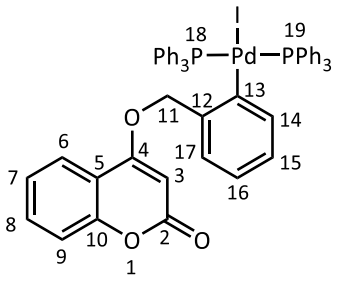
3-Methyl-1*H*,6*H*-pyrano[4,3-*c*]isochromene-1,6-dione (75)



To a reaction vial with a stir bar was added pyridinium chlorochromate (PCC) (20.5 mg, 1.5 equiv.). 3-Methylpyrano[4,3-*c*]isochromen-1(6*H*)-one **31** (13.6 mg, 1.0 equiv.) was dissolved in 1 mL DCE and added to the vial. The vial was capped and placed in an oil bath preheated to 84 °C. The reaction mixture was refluxed for 4 h, cooled to ambient temperature and filtered through a plug of celite, then a plug of silica with the aid of DCM. The crude product was a yellow solid consisting of both starting material and product (1.8:1.0 SM:P). The crude product was dissolved in 1 mL DCE and added to a fresh reaction vial containing PCC (22.5 mg, 1.5 equiv.). The reaction mixture was stirred at 84 °C for 4 days, then at ambient temperature for 3 days, and the reaction mixture was transferred onto a plug of silica and eluted with DCM to afford **75** as a tan solid (0.0041 g, 26%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (ddd, *J* = 8.3, 1.0, 0.5, 1H, C(10)**H**), 8.33 (ddd, *J* = 7.9, 1.5, 0.5, 1H, C(13)**H**), 7.87 (ddd, *J* = 8.3, 7.3, 1.5, 1H, C(12)**H**), 7.59 (ddd, *J* = 8.0, 7.4, 1.1, 1H C(11)**H**), 6.25 (d, *J* = 0.9, 1H, C(5)**H**), 2.39 (d, *J* = 0.8, 3H, C(7)$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (q**C**-6), 162.2 (q**C**-8), 160.4 (q**C**-4), 159.5 (q**C**-2), 136.0 (**C**(10)H), 133.1 (q**C**-14), 130.1 (**C**(13)H), 128.8 (**C**(12)H), 125.5 (**C**(11)H), 119.7 (q**C**-9), 99.4 (**C**(5)H), 98.9 (q**C**-3), 20.3 (**C**(7)H_3); *m/z* (ES-): 227 ($(M-H)^-$ 100%).

5.7. Isolation of oxidative addition intermediate 145

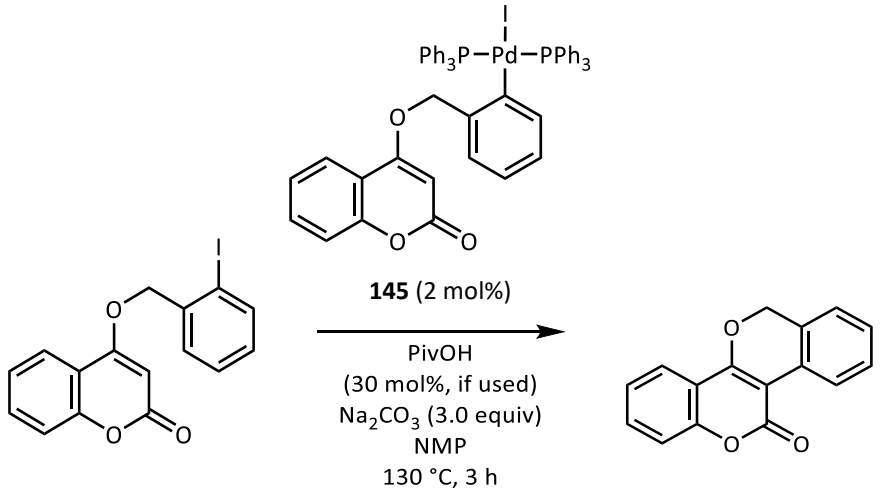
[Pd{(C_7H_6O-2-($C_9H_5O_2$))}I(PPh_3)$_2$] (145)



A Schlenk tube was heated under vacuum and refilled with N_2 three times. $Pd_2(dba)_3$ (42.4 mg, 0.046 mmol, 1.0 equiv.) and PPh_3 (97.0 mg, 0.370 mmol, 8.0 equiv.) were added. The Schlenk tube was evacuated and refilled with N_2 three times. Freshly distilled THF (10 mL) was added giving a brown solution. The reaction was stirred at ambient temperature for 15 min, resulting in a dark green solution. 4-((2-Iodobenzyl)oxy)-2*H*-chromen-2-one **20** (35.0 mg, 0.093 mmol, 2.0 equiv.) was added to the solution. The coumarin dissolved and the solution remained dark green. The Schlenk tube was placed in an oil bath preheated to 70 °C and stirred at this temperature for 1 h. The vessel was then cooled to ambient temperature and the reaction mixture concentrated under reduced pressure yielding a green residue. Et_2O (5 mL) was used to dissolve the residue. The solution was stored at 5–8 °C overnight. The resulting grey precipitate was isolated by suction filtration and dried under vacuum to yield **145** as a grey powder (42.1 mg, 90% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.41 (m, 13H, 13 × ArC**H**), 7.35 – 7.14 (m, 20H, 20 × ArC**H**), 7.08 – 7.00 (m, 1H, ArC**H**), 6.87 – 6.81 (m, 1H, ArC**H**), 6.64 – 6.57 (m, 2H, C(16)**H** & C(17)**H**), 6.37 – 6.30 (m, 1H, C(15)**H**), 5.64 (s, 1H, C(3)**H**), 4.85 (s, 2H, C(11)**H**$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5 (q**C**-4), 162.9 (q**C**-2), 161.3 (t, *J* = 3, q**C**-13), 153.3 (q**C**-10), 137.1 (t, *J* = 4, q**C**-Ar), 136.3 (t, *J* = 5, Ar**C**H), 134.7 (t, *J* = 6, 12 × Ar**C**H), 132.1 (Ar**C**H), 131.6 (t, *J* = 24, 6 × q**C**-Ar), 130.0 (6 × Ar**C**H), 128.7 (Ar**C**H), 127.9 (t, *J* = 5, 12 × Ar**C**H), 127.4 (Ar**C**H), 123.5 (Ar**C**H), 123.2 (Ar**C**H), 123.0 (Ar**C**H), 116.6 (Ar**C**H), 115.7 (q**C**-5), 90.4 (**C**(3)H), 74.3 (**C**(11)H$_2$); ^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$) δ: 22.8 (s, **P**-18 & **P**-19).

5.8. Procedures for mechanistic experiments

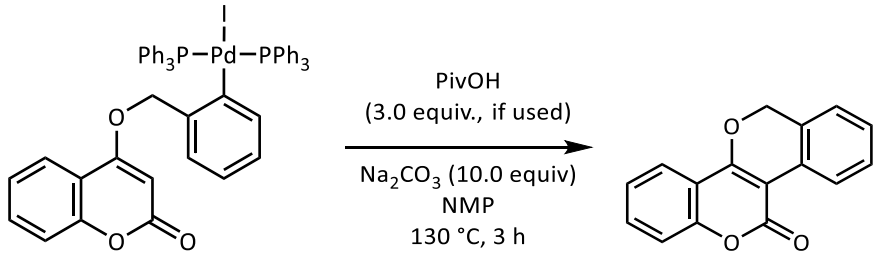
5.8.1. Use of oxidative addition product 145 as a catalyst



20 **38**

This experiment was conducted as per the General Procedure in **Section 5.3.1**, except that [Pd{(C_7H_6O-2-($C_9H_5O_2$))}I(PPh_3)$_2$] **145** (2.7 mg, 0.003 mmol, 2 mol%) was used instead of $Pd_2(dba)_3$ and PPh_3 with 4-((2-iodobenzyl)oxy)-2*H*-chromen-2-one **20** (50 mg, 0.132 mmol, 1.0 equiv.) as the substrate. The yield of **38** was determined from the ^{1}H NMR spectrum of the crude reaction mixture with 1,3,5-trimethoxybenzene as the internal standard for quantification. In the presence of PivOH, the yield of **38** was determined to be 55%. In the absence of PivOH, the yield of **38** was determined to be 3%.

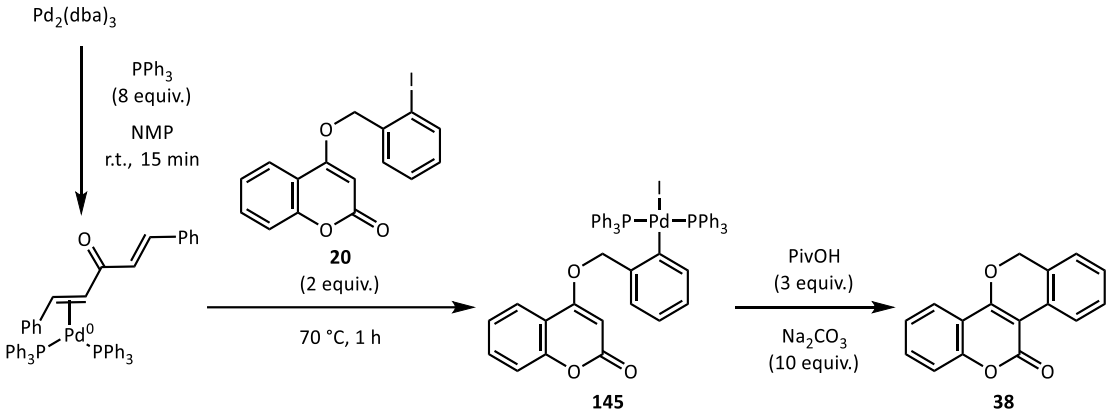
5.8.2. Investigation of the competence of oxidative addition product 145 to form the product 38 without additional substrate 20



145 **38**

A Schlenk tube was heated under vacuum and refilled with N_2 three times. Dry Na_2CO_3 (15.8 mg, 0.149 mmol, 10.0 equiv.) was added to a Schlenk tube. The Schlenk was then heated under vacuum and refilled with N_2 twice. [Pd{(C_7H_6O-2-($C_9H_5O_2$))}I(PPh_3)$_2$] **145** (15.0 mg, 0.0.015 mmol, 1.0 equiv.) and PivOH (4.6 mg, 0.045 mmol, 3.0 equiv., if used) were then added. The Schlenk was then evacuated and refilled with N_2 twice. Anhydrous NMP (1 mL) was added and the reaction mixture was placed in an oil bath preheated to 130 °C. After 3 hours, the mixture was allowed to cool to room temperature and diluted with water (10 mL) and EtOAc (10 mL). The organic layers were extracted with EtOAc (2 × 10 mL) and washed with 1 M aqueous HCl (1 × 20 mL), H_2O (3 × 10 mL) and brine (1 × 20 mL). The combined organic extracts were dried, filtered and concentrated under reduced pressure. The yield of **38** was determined from the ^{1}H NMR spectrum of the crude reaction mixture with 1,3,5-trimethoxybenzene as the internal standard for quantification. In the presence of PivOH, the yield of **38** was determined to be 36%. In the absence of PivOH, the yield was determined to be 5%.

5.8.3. Detection of oxidative addition product 145 in reaction solvent



A Schlenk tube was heated under vacuum and refilled with N_2 three times. $Pd_2(dba)_3$ (48.4 mg, 0.053 mmol, 1.0 equiv.) and PPh_3 (111.0 mg, 0.423 mmol, 8.0 equiv.) were then added. The Schlenk was then evacuated and refilled with N_2 three times. Anhydrous NMP (2 mL) was added giving a dark green solution. The reaction was stirred at ambient temperature for 15 minutes. 4((2-Iodobenzyl)oxy)-2*H*-chromen-2-one **20** (40 mg, 0.106 mmol, 1.0 equiv.) was added to the NMP solution. The coumarin dissolved and the solution remained dark green. The reaction mixture was heated to 70 °C and stirred at this temperature for 1 h. 0.1 mL of the reaction mixture was removed at this point and analysed using ^{1}H and $^{31}P\{^{1}H\}$ NMR to confirm the presence of the oxidative addition intermediate **145**. PivOH (16.2 mg, 0.159 mmol, 3.0 equiv.) and Na_2CO_3 (56.1 mg, 0.529 mmol, 10.0 equiv.) were then added to the reaction mixture. The reaction was then heated to 130 °C and stirred at this temperature for a further 3 h. The mixture was then allowed to cool to ambient temperature and diluted with water (10 mL) and EtOAc (10 mL). The organic layers were extracted with EtOAc (2 × 10 mL) and washed with 1 M aqueous HCl (1 × 20 mL), H_2O (3 × 10 mL) and brine (1 × 20 mL). The combined organic extracts were dried, filtered and concentrated under reduced pressure. The yield of **38** was determined to be 47% from the ^{1}H NMR spectrum of the crude reaction mixture with 1,3,5-trimethoxybenzene as the internal standard for quantification.

5.8.4. Determination of kinetic isotope effect at C–3 for the formation of 6*H*,11*H*-isochromeno[4,3-*c*]chromen-11-one (38)

Using a Carousel® parallel reactor, 12 reaction tubes were heated at 140 °C under vacuum for 30 min, then refilled with N_2. The hot tubes were then evacuated and refilled with N_2 twice more. Na_2CO_3 (79.0 mg, 0.750 mmol, 3.0 equiv.) was added to each tube. The hot tubes were evacuated and refilled with N_2 twice. The heat was turned off and the tubes were allowed to cool to ambient temperature under N_2. To each of the 12 tubes was added $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol, 2 mol%), PPh_3 (2.6 mg, 0.010 mmol, 4 mol%) and PivOH (7.7 mg, 0.075 mmol, 30 mol%). To 6 of the tubes was added 4-((2-iodobenzyl)oxy)-2*H*-chromen-2-one **20** (95.0 mg, 0.250 mmol, 1.0 equiv.), and to the other 6 tubes was added 4-((2-iodobenzyl)oxy)-2*H*-chromen-2-one-3-d **148** (95.0 mg, 0.250 mmol, 1.0 equiv.). The 12 tubes were evacuated and refilled with N_2 three times. The hot plate was set to heat to 130 °C while anhydrous NMP (2 mL) was added to each tube. Each tube was sealed off from the N_2 inlet after NMP addition. When the addition of NMP to the final tube was complete, the hot plate had reached the desired temperature (t = 0). The reactions were quenched in pairs (one non-deuterated, one deuterated) by adding H_2O (10 mL) at the following time points: 5 min, 10 min, 20 min, 45 min, 90 min, 180 min. The quenched reactions were removed from the Carousel® and cooled to ambient temperature. Each mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers for each mixture were washed with 1 M aqueous HCl (1 × 20 mL), H_2O (3 × 10 mL) and brine (1 × 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure.

Each crude reaction mixture was analysed by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard for quantification. This set of reactions was performed twice and the data from the two runs were averaged. The yields of 6*H*,11*H*-benzofuro[4,3-*c*]chromen-11-one **38** were plotted against reaction time to give the plot shown in **Figure 4.2**.

5.8.5. Determination of intramolecular kinetic isotope effect for 3-bromo-2-pyrone direct arylation

K_2CO_3 (0.15 g, 1.07 mmol) was added to a Schlenk tube. The Schlenk tube was then heated under vacuum using a heat gun and refilled with N_2. This was repeated twice more and the Schlenk tube was allowed to cool. 3-Bromo-4-(2-deuterio)phenoxy-6-methyl-2*H*-pyran-2-one **152** (0.10 g, 0.36 mmol), $Pd(OAc)_2$ (0.004 g, 0.02 mmol) and PPh_3 (0.014 g, 0.05 mmol) were then added. The reagents were then stirred under vacuum and the Schlenk tube was refilled with N_2. This procedure was repeated twice more. Xylenes (1 mL/0.25 mmol) was then added. The reaction was heated to 130 °C and stirred for 15 hours. Upon cooling, the reaction was diluted with water (15 mL) and EtOAc (15mL). The mixture was extracted with EtOAc (2 × 15 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residues were purified by column chromatography (EtOAc:hexanes 4:96). A ^{1}H NMR spectrum of the isolated product was recorded. The ratio of non-deuterated to deuterated product was used to determine the KIE, as shown in **Figure 4.3**.

5.8.6. Determination of kinetic isotope effect for C–3 position in double C–H activation

Following the reported methodology,[12] six identical reactions were set side-by-side. Each reaction tube was charged with 4-phenoxy-2*H*-chromen-2-one **97** (50 mg, 0.21 mmol), $Pd(OAc)_2$ (4.7 mg, 0.02 mmol), NaO*t*Bu (4.0 mg, 0.04 mmol), Ag_2O (73 mg, 0.31 mmol) and PivOH (0.5 M). The reactions were stirred at 120 °C in air and stopped at 5, 10, 20, 40, 60 and 120 min, respectively. In a parallel experiment, six reactions were performed using 3-deuterio-4-phenoxy-2*H*-chromen-2-one **156** (50 mg, 0.21 mmol) as a substrate under otherwise identical conditions. Each of the reactions was diluted with DCM and filtered through a pad of celite. The organic layers were washed with 10% (w/v) aqueous NaOH, dried over $MgSO_4$ and concentrated under reduced pressure.

The crude reaction mixture was analysed by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard for quantification. This set of experiments was performed twice, and the data from the two runs were averaged. The yields of 6*H*-

benzofuro[3,2-*c*]chromen-6-one **154** were plotted against reaction time to give the plot shown in **Figure 4.7**.

5.8.7. Determination of kinetic isotope effect for aryl C–H position in double C–H activation

Experiment 1

A reaction tube was charged with 5-methoxy-4-phenoxy-2*H*-chromen-2-one **162** (40 mg, 0.150 mmol), $Pd(OAc)_2$ (3.4 mg, 0.0150 mmol), NaO*t*Bu (2.9 mg, 0.030 mmol), Ag_2O (52.1 mg, 0.225 mmol) and PivOH (889 mg, 1 mL). The reaction mixture was stirred at 120 °C in air. In a parallel experiment, a reaction was performed using 5-methoxy-4-(phenoxy-d_5)-2*H*-chromen-2-one **165** (41 mg, 0.150 mmol) as a substrate under otherwise identical conditions. After 5, 10, 20 and 40 mins, a sample was simultaneously removed from both reactions. The sample was diluted with DCM and filtered through a pad of celite. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure.

The crude reaction mixtures were analysed by ^{1}H NMR. The % conversion from starting material to 1-methoxy-6*H*-benzofuro[3,2-*c*]chromen-6-one **167** for each sample was determined. This set of reactions was performed twice, and the data from the two runs were averaged. % Conversion was plotted against reaction time to give the plot shown in **Figure 4.9**.

Experiment 2

A reaction tube was charged with 5,7-dimethyl-4-phenoxy-2*H*-chromen-2-one **164** (26.6 mg, 0.10 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), NaO*t*Bu (1.9 mg, 0.02 mmol), Ag_2O (34.8 mg, 0.15 mmol) and PivOH (889 mg, 1 mL). The reaction was stirred at 120 °C in air. In a parallel experiment, a reaction was performed using 5,7-dimethyl-4-(phenoxy-d_5)-2*H*-chromen-2-one **166** (27.1 mg, 0.10 mmol) as a substrate under otherwise identical conditions. After 5, 10, 20 and 40 mins, a sample was simultaneously removed from both reactions. The sample was diluted with DCM and filtered through a pad of celite. The organic layers were concentrated under reduced pressure.

The crude reaction mixtures were analysed by ^{1}H NMR. The % conversion to 1,3-dimethyl-6*H*-benzofuro[3,2-*c*]chromen-6-one **168** for each sample was plotted against reaction time to give the plot shown in **Figure 4.10**.

5.8.8. Scrambling experiment

A reaction tube was charged with 4-phenoxy(-d_5)-2*H*-chromen-2-one **157** (50 mg, 0.21 mmol), $Pd(OAc)_2$ (4.7 mg, 0.02 mmol), NaO*t*Bu (4.0 mg, 0.04 mmol), Ag_2O (73 mg, 0.31 mmol) and PivOH (0.5 M). The reaction was stirred at 140 °C in air for 2 h, then cooled to ambient temperature, diluted with DCM and filtered through a pad of celite. The organic layers were washed with 10% (w/v) aqueous NaOH, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was then flushed through silica gel using DCM as eluent to afford the product, which was purified by recrystallisation from DCM/hexanes and analysed by ^{1}H NMR to give the spectrum shown in **Figure 4.8**.

5.9. References

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Appendix I

List of Publications

Paper I: "Pd/Pivalic Acid Mediated Direct Arylation of 2-Pyrones and Related Heterocycles". Pardo, L. M., Prendergast, A. M., Nolan, M.-T., Ó Muimhneacháin, E., McGlacken, G. P. *Eur. J. Org. Chem.* **2015**, 3540-3550. Copyright 2015 John Wiley & Sons.

Paper II: "Intramolecular Direct Arylation of 3-Halo-2-pyrones and 2-Coumarins". Nolan, M.-T., Pardo, L. M., Prendergast, A. M., McGlacken, G. P. *J. Org. Chem.* **2015**, *80*, 10904–10913. Copyright 2015 American Chemical Society.

Paper III: "Cyclization of 4-Phenoxy-2-coumarins and 2-Pyrones via a Double C–H Activation". Mackey, K., Pardo, L. M., Prendergast, A. M., Nolan, M.-T., Bateman, L. M., McGlacken, G. P. *Org. Lett.* **2016**, *18*, 2540-2543. Copyright 2016 American Chemical Society.

Paper IV: "Regioselective Chlorination and Suzuki-Miyaura Cross-Coupling of 4-Alkoxycoumarins, 4-Alkoxy-2-Pyrones and Related Heterocycles". Prendergast, A. M. and McGlacken, G. P. *Eur. J. Org. Chem.* **2017**, 4827-4835. Copyright 2017 John Wiley & Sons.

Paper V: "Access to Some C5-Cyclised 2-Pyrones and 2-Pyridones via Direct Arylation; Retention of Chloride as a Synthetic Handle". Prendergast, A. M., Pardo, L. M., Fairlamb, I. J. S. and McGlacken, G. P. *Eur. J. Org. Chem.* **2017**, 5119-5124. Copyright 2017 John Wiley & Sons.

Paper VI: "Mechanistic studies on the palladium-catalyzed cross-dehydrogenative coupling of 4-phenoxy-2-coumarins: experimental and computational Insights". Prendergast, A. M., Zhang, Z., Lin, Z. and McGlacken, G. P. *Dalton Trans.* **2018**, 10.1039/c8dt00842f. Copyright 2018 Royal Society of Chemistry.

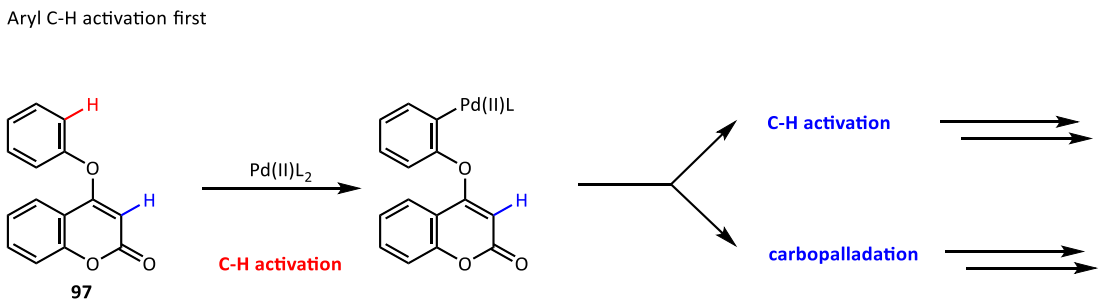
Paper VII: "Transition Metal-Mediated C–H Activation of 2-Pyrones, 2-Pyridones, 2-Coumarins and 2-Quinolones". Prendergast, A. M. and McGlacken, G. P. *Eur. J. Org. Chem.* **2018**, 10.1002/ejoc.201800299. Copyright 2018 John Wiley & Sons.

Appendix II

Other mechanisms for CDC of 4-phenoxy-2-coumarins

Several mechanistic modes of action were considered possible for the CDC of 4-phenoxy-2-coumarins. The most likely mechanistic pathway is discussed in **Section 4.4.5**. In addition to that pathway, other pathways were considered but discounted. It is these pathways which are discussed in this Appendix.

The activation of the aryl C–H bond could occur before coumarin C–3–H activation, as in **Scheme I**. A CMD pathway[1] and a carbopalladation pathway[2] were both considered as possibilities for this sequence of activation.



Scheme I. Mechanistic possibilities investigated for Pd-catalysed CDC of 4-phenoxy-2-coumarin.

The CMD pathway shown in **Scheme I** was calculated using DFT (**Figure I**).

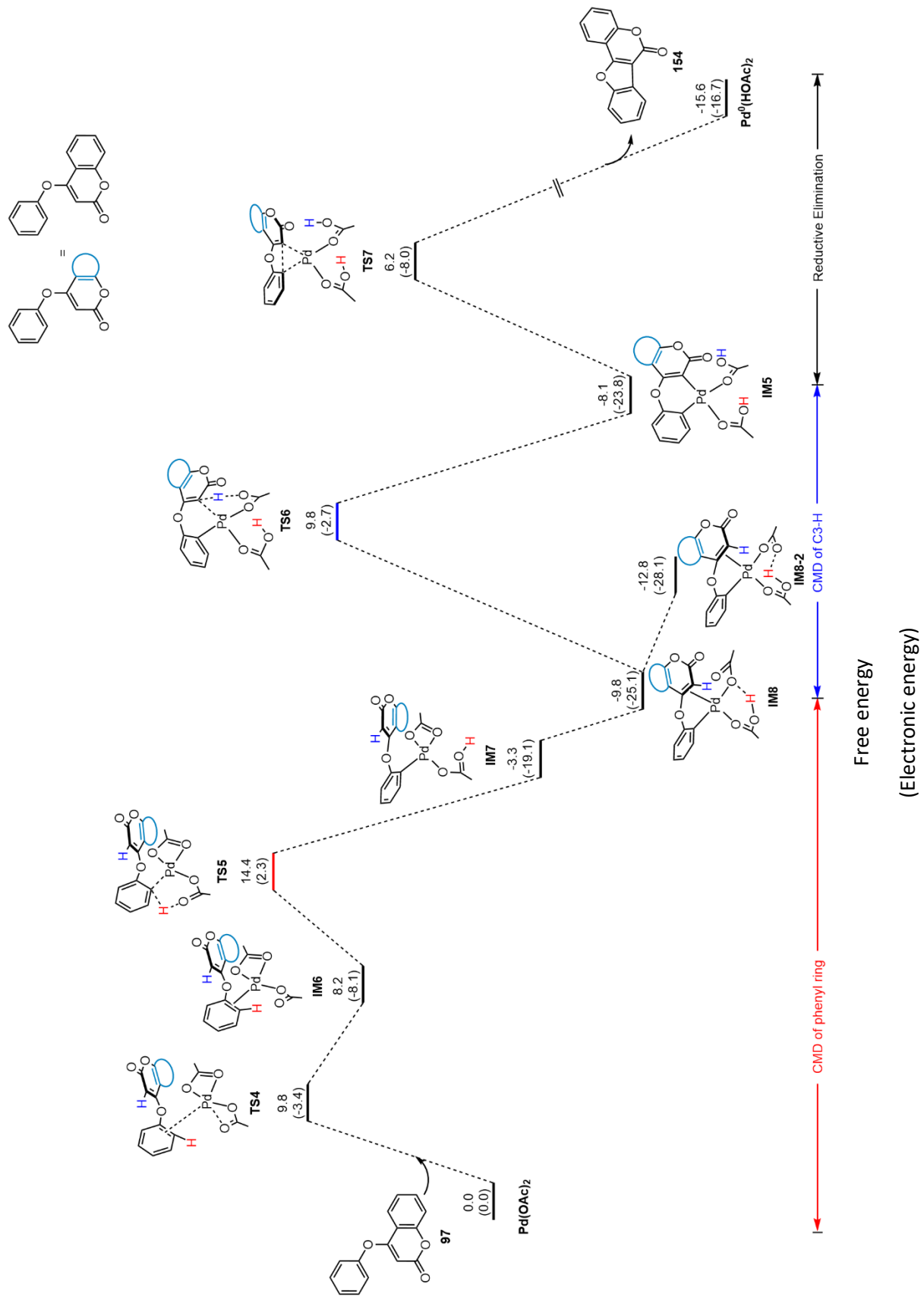


Figure I. DFT calculations for the direct arylation of **97** to **154** *via* double C–H activation. Pathway (a) shows that CMD of phenyl ring happens first.

This pathway was calculated to begin with an κ^2-κ^1 displacement of an acetate ligand (**TS4**, $\Delta G^{\ddagger}$ = 9.8 kcal mol^{-1}) to give a π-complex **IM6**. The structure of this intermediate only shows small distortion, which cannot be regarded as Wheland intermediate, thus ruling out an S_EAr mechanism.[1, 3-4] **IM6** is followed by a CMD[5] transition state **TS5** ($\Delta G^{\ddagger}$ = 6.2 kcal mol^{-1}) which generates **IM7**. **TS5** represents the summit of the potential energy surface for this pathway, which is consistent with the observed primary positive KIE of 3 for the cleavage of the aryl C–H bond.

After interconversion from **IM7** to the π-complex **IM8**, the acetate ligand could rotate to coordinate to the hydrogen of the other acetate acid ligand to generate **IM3-2** (ΔG = −12.8 kcal mol^{-1}) *via* a stronger intramolecular hydrogen bond which confers additional stability.[6] An acetate ligand abstracts the C–3 proton from the 2-coumarin (**Figure I**, blue hydrogen) *via* a second CMD transition state **TS6** ($\Delta G^{\ddagger}$ = 22.6 kcal mol^{-1}) to generate **IM5**. **IM5** is also calculated to exist in the DFT calculation shown in **Figure 4.11**.

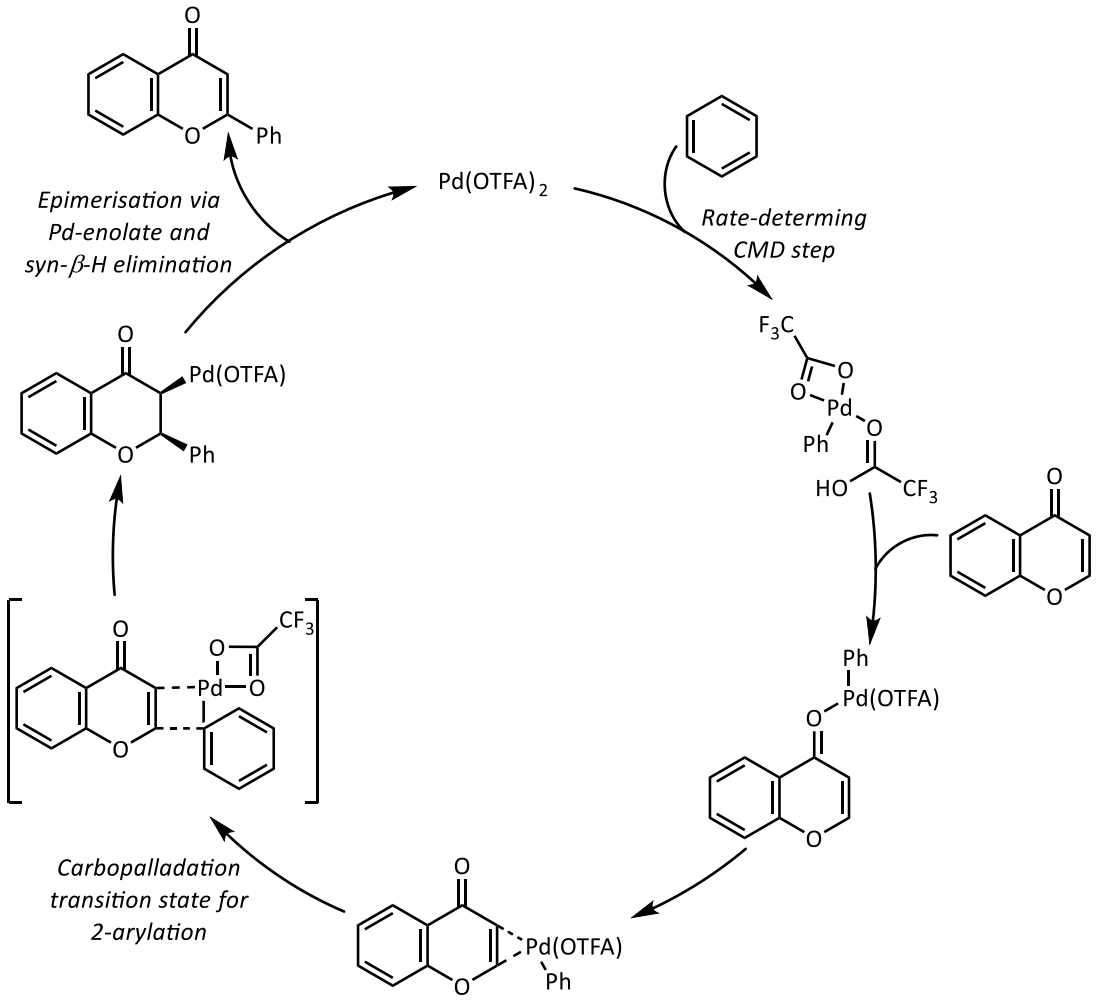
The palladation and C–H cleavage at the C–3 position is not calculated to be reversible in this pathway due to the energy barrier between intermediates **IM8** and **IM5**. Additionally, the relatively facile reductive elimination (**TS7**, $\Delta G^{\ddagger}$ = 21.8 kcal mol^{-1}) is likely irreversible. This conflicts with the experimental evidence which shows that palladium-mediated H/D exchange is reversible at the C–3 position (**Figure 4.4** and **Figure 4.5**).

The reductive elimination (**TS7**, $\Delta G^{\ddagger}$ = 21.8 kcal mol^{-1}) releases product **154** and the palladium complex Pd(0)$(HOAc)_2$. The proton on the acetic acid ligand could transfer to a Brønsted base such as *tert*-butoxide (*t*BuO$^-$) or pivalate (PivO$^-$), while Pd(0) is likely oxidised to Pd(II) by Ag_2O. It is difficult to study the oxidation step in a meaningful way as there are no reasonable structural models for Ag_2O at this time.

The summit of the potential energy surfaces for both DFT calculations can be compared. The summit of the potential energy surface for the pathway shown in **Figure 4.11** is **TS2** (ΔG = 12.2 kcal mol^{-1}) which is lower than the summit of the other pathway (**Figure I**, **TS5,** ΔG = 14.4 kcal mol^{-1}). The pathway in **Figure 4.11** is therefore more favourable by 2.2 kcal mol (in the free energy barrier).

In general, it would seem unlikely that this is the operative mechanism due to the conflicts between the experimental evidence and the computational data.

Next, it was important to consider carbopalladation (**Scheme I**) as a possible mechanism for the CDC of 4-phenoxy-2-coumarins due to the similarities between 2-coumarins and 4-chromones. A carbopalladation pathway has been reported for the arylation of 4-chromones by Choi *et al.* (**Scheme II**).[2] The objective of their computational work was to explain the experimentally observed regioselectivity of 4-chromone arylation, in favour of 2-arylation.



Scheme II. Mechanism of chromone arylation proposed by Choi *et al.*[2]

The C–H activation of benzene was computed to occur more quickly than the C–H activation at either the C–2 or C–3 position of chromone. Additionally, the resultant phenylpalladium species is more stable than the analogous intermediate at either

position of chromone. Since arylpalladium species were known experimentally to add across the π-bonds of enones, a carbopalladation of the phenylpalladium intermediate across the isolated π-bond of chromone was investigated by Choi *et al*.[2] Two carbopalladation transition states were identified (one for the 2-arylated product (**Scheme II**) and one for the 3-arylated product) and it was confirmed that there was no feasible means of interconversion between the two adducts, meaning that carbopalladation was the regioselective step. The greater π-electron density at the C–3 position of chromone favours the delivery of the electrophilic Pd(OTFA) centre to this position, which leads to the C–2 delivery of the phenyl group in the carbopalladation step (**Scheme II**). The experimentally observed KIE of 2.90 for benzene-h_6/d_6 agrees with the computed turnover-limiting C–H cleavage of benzene. These carbopalladation transition states were found to lie much lower in energy (>7 kcal mol^{-1}) than the structures obtained for a sequential CMD pathway, lending support for a carbopalladation pathway. The calculations showed that the steps following carbopalladation were relatively facile, rendering carbopalladation irreversible and therefore the regiodetermining step in chromone arylation.

In our case, the electrophilic Pd species also prefers to approach the C–3 position due to the greater π-electron density, consistent with the calculations described by Choi *et al.*[2] This electronic preference of Pd for the C–3 position restricts the ability of the aryl ring to approach the C–3 position to give the observed product **154**. In order to achieve our observed product **154**, Pd would need to approach either C–2 or C–4. Since the phenyl ring of the arylpalladium intermediate **IM7** is connected to the 2-coumarin through an oxygen atom, a conformation to fulfil a carbopalladation-type addition could not be found (**Figure II**). This is in contast to Choi *et al.*'s report which describes an intermolecular reaction.[2]

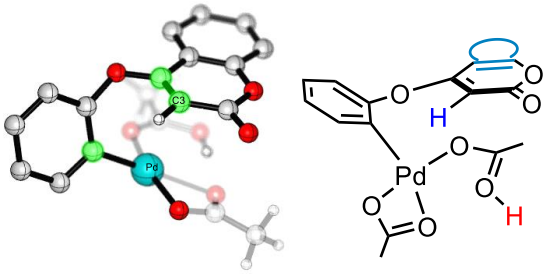


Figure II. The optimised structure **IM7**. Some hydrogen atoms are omitted for clarity.

Overall, this data seems to render a carbopalladation mechanism for the CDC of 4-phenoxy-2-coumarin (**97**) unlikely.

Having identified conflicts between the experimental observations and the computational data for both of the mechanistic modes shown in **Scheme I**, these mechanisms were considered unlikely. The available experimental and computational evidence at this time indicates that the mechanistic proposal shown in **Scheme 4.34** (**Section 4.4.5**) is most likely to be operative.

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